

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
26 August 2004 (26.08.2004)

PCT

(10) International Publication Number
WO 2004/071454 A2

(51) International Patent Classification⁷: **A61K**
(21) International Application Number:
PCT/US2004/004222
(22) International Filing Date: 13 February 2004 (13.02.2004)
(25) Filing Language: English
(26) Publication Language: English
(30) Priority Data:
60/447,319 13 February 2003 (13.02.2003) US

(71) Applicant (for all designated States except US): **GUILFORD PHARMACEUTICALS INC.** [US/US]; 6611 Tributary Street, Baltimore, MD 21224 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LI, Weixing** [US/US]; 9804 Madelaine Court, Ellicott City, MD 21042 (US). **OLIVER, Eddie, Jr.** [US/US]; 5309 Moravia Road, Apt. J., Baltimore, MD 21206 (US). **ROJAS, Camilo** [US/US]; 1204 Roundhill Road, Baltimore, MD 21218 (US). **KALISH, Vincent** [US/US]; 344 Dubois Road, Annapolis, MD 21401 (US). **BELYAKOV, Sergei** [UA/US]; 9500 Midaro Court, Baltimore, MD 21236 (US).

(74) Agents: **SAUER, Hansjorg et al.**; Guilford Pharmaceuticals Inc., 6611 Tributary Street, Baltimore, MD 21224 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 2004/071454 A2

(54) Title: SUBSTITUTED AZETIDINE COMPOUNDS AS INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

(57) Abstract: Novel azetidine-derived inhibitors of dipeptidyl peptidase IV (DPP IV), pharmaceutical compositions comprising therapeutically effective amounts of such inhibitors, and novel methods of treating medical conditions are provided. The novel DPP IV inhibitors described herein feature an azetidine ring substituted with one or more groups selected from fluoro-, di-fluoro, oxo-, cyano, alkoxy, and alkyl, and are useful in the treatment of neurological disorders, mental illness, diabetes, inflammatory disorders such as arthritis, obesity, osteoporosis, and of such other medical conditions as can be treated with inhibitors of DPP IV.

Substituted Azetidine Compounds as Inhibitors of Dipeptidyl Peptidase IV

The present invention relates to new and improved inhibitors of Dipeptidyl Peptidase IV, and new and improved treatment methods and related uses. The novel DPP
5 IV inhibitors described herein feature an azetidine ring substituted with one or more groups selected from fluoro-, di-fluoro, oxo-, cyano, alkoxy, and alkyl, and are useful in the treatment of a wide variety of diseases and other abnormal conditions, including neurological disorders, diabetes, inflammatory disorders such as arthritis, obesity, osteoporosis, and other medical conditions.

10 Dipeptidyl peptidase IV (DPP IV, EC 3.4.14.5) is a membrane-anchored aminopeptidase involved in the release of N-terminal dipeptides from proteins and other types or forms of peptides. The enzyme is a type II membrane serine peptidase, and has a substrate preference for proteins or peptides which carry a proline at the penultimate position of their N-termini. Since the peptide bonds before and after proline residues are
15 known to be relatively resistant to cleavage by common proteases, it has been speculated that the presence of proline at the penultimate position of the peptide chain – a feature shared by a number of immunopeptides, neuropeptides, and peptide hormones - protects such peptides from degradation by unspecific exopeptidases. A physiological role for DPP IV has been assumed to be in the activation, inactivation, or degradation of its
20 substrates through the specific release of a proline-containing dipeptide from the N-terminal region of the substrate peptide.

DPP IV has been found in the kidney, epithelial cells, endothelial cells, small intestine, prostate, brain, placenta, and liver. In T-cells, it has been shown to be identical to the memory cell surface antigen CD26. Other proteins which display DPP IV-like
25 activity include fibroblast-activation protein (FAP), an inducible type-II cell-surface glycoprotein selectively expressed by reactive stromal fibroblasts of epithelial cancers and healing wounds [Niedermeyer, *et al.*, *Eur. J. Biochem.* 1998 254 (1998):650-4] and attractin/mahogany protein, which exists in membrane-bound and secreted forms and is implicated in control of pigmentation, energy metabolism, and CNS myelination [Tang *et al.*, *Proc. Natl. Acad. Sci. U. S. A.* 97 (2000) 6025-30.].
30

DPP IV activity has also been found in serum, urine, seminal plasma, and amniotic fluid. It has been speculated that this soluble DPP IV activity can be attributed to cleavage of the membrane-bound form of DPP IV and release of its catalytic portion into the bloodstream [Augustyns, K., *et al.*, *Current Medicinal Chemistry*, 6 (1999) 311-

327]. Additionally, a distinct form of DPP IV, which appears to be a breakdown product of the T-cell surface antigen DPPT-L, has been described in human plasma. [Duke-Cohan, *et al.*, *J. Immunol.* 156 (1996) 1714-21].

The physiological roles of DPP IV have not been completely elucidated. It has
5 been thought that DPP IV plays a role, amongst others, in the regulation of fat intake, natriuresis, nociception, T-cell activation, regulation of blood glucose, and regulation of the digestive tract. DPP IV has been implicated in disease states such as HIV infection, diabetes, arthritis and certain cancers. For example, DPP IV activity and/or expression was found to be elevated in prostate [Wilson, *et al.*, *J. Androl.* 21 (2000) 220-6], colon
10 [Fric, *et al.*, *Eur. J. Cancer Prev.* 9 (2000):265-8], skin [Van den Oord, *Br. J. Dermatol.* 138 (1998) 615-21] and lung cancer [Sedo, *et al.*, *J. Cancer Res. Clin. Oncol.* 117 (1991) 249-53], and elevated DPP IV also has been found in patients having benign prostate hyperplasia. A high activity of DPP IV is also associated with membrane vesicles found in human, bovine, and equine ejaculate, where it is thought to play a role in the regulation
15 of sperm motility and viability [Minelli A, *et al.*, *J. Reprod. Fertil.* 114 (1998) 237-43; Agrawal, *et al.*, *J. Reprod. Fertil.* 79 (1987) 409-19; Arienti, *et al.*, *FEBS Lett.* 410 (1997) 343-6].

DPP IV also is being investigated for its role in type II diabetes because the glucagon-like peptide (GLP-1) can be a substrate for DPP IV cleavage, and some DPP IV
20 inhibitors have demonstrated efficacy in animal models of diabetes. Additionally, DPP IV has been implicated in HIV infection due to its association with CD 26.

High levels of DPP IV expression have been reported for skin fibroblasts from human patients suffering from psoriasis, rheumatoid arthritis, and lichen planus [Raynaud, *et al.*, *J. Cell Physiol.* 151 (1992) 378]. Inhibition of DPP IV has been shown
25 to increase release of TGF- β , a protein having neuroprotective properties. DPP IV inhibition itself has been implicated in cellular mechanisms relating to neurodegeneration [see PCT publication WO 01/34594].

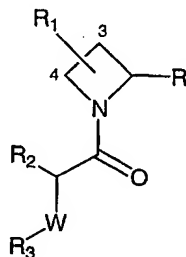
It follows from the above that inhibitors of DPP IV may be useful as
pharmaceuticals in the treatment of a range of medical conditions. In particular, they may
30 be useful as immunosuppressants, anti-inflammatory agents, drugs that suppress tumor invasion and metastasis formation, drugs that inhibit HIV infectivity, regulators of blood glucose levels in patients suffering from diabetes, agents that affect sperm motility and viability useful both for contraception and in the reproduction of livestock, drugs for the

treatment of dermatological disorders such as psoriasis, and as pharmaceuticals for the treatment of neurological disorders.

DPP IV inhibition has been studied in the treatment of autoimmune diseases such as diabetes, arthritis and multiple sclerosis. See PCT publications WO 97/40832 and WO 98/19998. Additionally, PCT publication WO 94/03055 discusses increasing production of hematopoietic cells with DPP IV inhibitors. PCT publication WO 95/11689 discloses the use of DPP IV inhibitors to block the entry of HIV into cells. U.S. Patent No. 5,543,396 discloses the use of inhibitors (certain proline phosphonate derivatives) to treat tumor invasion. PCT publication WO 95/34538 mentions the use of certain serine protease inhibitors (such as certain DPP IV and PEP inhibitors) to treat inflammation-related neurological/autoimmune diseases like multiple sclerosis. Efficacy in experimental models of inflammatory disorders has also been described for compounds with DPP IV inhibitory activity, suggesting that such compounds may be useful in the treatment of medical conditions such as rheumatoid arthritis and inflammatory bowel disorder. Augustyns *et al.* (*Curr. Med. Chem.* 6 (1999) 311-327) and Hildebrandt *et al.* (*Clinical Science* 99 (2000) 93-104) review the wide therapeutic potential of various classes of DPP IV inhibitors.

DPP IV inhibitors based upon molecules that bear a resemblance to proline have been investigated in the field. For example, PCT publication WO 95/11689 discloses α -amino boronic acid analogs of proline. PCT publication WO 98/19998 discloses N-substituted 2-cyanopyrrolidines as DPP IV inhibitors. PCT publication WO 95/34538 discloses various proline containing compounds and phosphonate derivatives thereof. Proline phosphonate derivatives as inhibitors of DPP IV are also disclosed in U.S. Patent 5,543,396. U.S. Patent 6,172,081 discloses a series of tetrahydroisoquinoline 3-carboxamide derivatives with potent DPP-IV inhibitory activity; U.S. Patents 6,166,063 and 6,107,317 disclose N-substituted 2-cyanopyrrolidines and 4-cyanothiazolidines, respectively. WO 95/15309 discloses various aminoacyl compounds as inhibitors of DPP IV. WO 01/68603 discloses a class of cyclopropyl-fused pyrrolidine derivatives as inhibitors of DPP IV. N-substituted 2-cyanopyrrole derivatives as inhibitors of DPP IV, and pharmaceutical compositions thereof, are taught for the treatment of various metabolic disorders in U.S. Patent Application Publication 2001/0031780. A class of cyanoazetidine compounds is taught in WO 03/057666 to Guilford Pharmaceuticals. Additionally, WO 04/007446 to Yamanouchi (in Japanese) teaches certain cyano- and fluorocyanoazetidine compounds for use in inhibiting DPP-IV.

In view of the need to provide new therapeutic products, methodologies, and uses, this invention provides novel inhibitors of dipetidyl peptidase, which comprise compounds of the following Formula I:



Formula I

- or pharmaceutically acceptable derivatives thereof; wherein
 R is H or CN;
 R1 is F, di-F, (=O), CN, alkoxy, or alkyl, and is attached at position 3 or 4;
 W is NH, or CH₂;
- wherein, when W is NH:
- (i.) one of R2 and R3 is hydrogen, and the other of R2 and R3 is
 a C₁-C₁₂ straight or branched chain alkyl; or
 a C₁-C₆ straight or branched chain alkyl substituted with aryl,
 arylamino, heteroaryl, or heteroarylamino; or
 a saturated mono- bi- or tricyclic hydrocarbon wherein the
 individual rings comprise 3 – 12 carbon atoms; or
 - (ii.) R2 and R3, together with W and the carbon atom to which they are
 attached, form a four- to twelve-membered saturated ring, said ring
 optionally having fused thereto one or two additional rings
 independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂
 cycloalkenyl, aryl, and heteroaryl; and
- wherein, when W is CH₂:
- R2 and R3, together with W and the carbon atom to which they are
 attached, form a four- to twelve-membered heterocyclic ring, said
 ring containing at least one nitrogen immediately adjacent to W,
 said ring optionally having fused thereto one or two additional

rings independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂ cycloalkenyl, aryl, and heteroaryl;

provided that: when R is H, R1 is not CN attached at position 4;

and further provided that: when R is CN; and R1 is F or CN attached at position
5 3; and W is NH; then R3 is not adamantyl, bicyclooctyl, or 2-[(5-cyano-2-pyridyl)amino]ethyl.

In a preferred embodiment of the compounds of this invention, R is CN, R1 is attached at position 3, and represents F or di-F. More preferably, W in such compounds is
10 NH, R3 is H, and R2 is a C₃-C₁₂ straight or branched chain alkyl. Alternatively, R2 in such compounds is H and R3 represents a saturated mono-, di-, or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.

Other preferred embodiments of the compounds of the present invention are those where R is CN, and R1 is alkyl, more preferably methyl, attached at position 4. In such
15 preferred compounds, W is more preferably NH, and R2 and R3 together with W and the carbon atoms to which they are attached form a four to twelve-membered saturated ring which has optionally fused thereto one or two additional rings independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂ cycloalkenyl, aryl, and heteroaryl. Alternatively, R3 in
20 such preferred compounds is H, and R2 is a C₃-C₁₂ straight or branched chain alkyl, or a saturated mono-, di-, or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms. Yet other alternative embodiments of such preferred compounds are those wherein R2 is H and R3 is a C₃-C₁₂ straight or branched chain alkyl.

Other preferred embodiments of the compounds of this invention are those where R is H, R1 is F attached at position 3, W is NH, R3 is H, and R2 is a saturated mono-, di-,
25 or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.

Other preferred embodiments of the compounds of the invention are those compounds of Formula I wherein R is H, and R1 is alkoxy attached at position 3. More preferably, W is NH and R3 in such compounds is H, and R2 is a saturated mono-, di-, or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.

30 Other preferred embodiments of the compounds of this invention are compounds of Formula I wherein R is H and R1 is (=O) attached at position 4. More preferably, W in such compounds is NH, and R2 and R3 together with the nitrogen and carbon atoms to which they are attached form a four to twelve-membered saturated ring which has

optionally fused thereto one or two additional rings independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂ cycloalkenyl, aryl, and heteroaryl.

Yet other preferred embodiments of the compounds of the instant invention are compounds of Formula I wherein R is H and R₁ is (=O) attached at position 3. More preferably, W in such compounds is NH, R₃ is H, and R₂ is a saturated mono-, di-, or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.

In another aspect of this invention, there is provided a method of treating a medical condition, comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula I, or of any of the above-described preferred embodiments of the compounds of Formula I, or of pharmaceutically acceptable derivatives thereof. In a preferred embodiment of this aspect of the invention, the medical condition to be treated is a medical condition which can be alleviated by inhibition of DPP IV.

The present invention further provides a method of inhibiting DPP IV in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of Formula I, or of any of the above-described preferred embodiments of the compounds of Formula I, or of pharmaceutically acceptable derivatives thereof.

Also included in the present invention are pharmaceutical compositions useful in the treatment of medical conditions, or in inhibiting DPP IV, which comprise a therapeutically effective amount of one or several compounds of Formula I, or of one or several of the above-described preferred embodiments of the compounds of Formula I, or of pharmaceutically acceptable derivatives thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

Compounds of Formula I may be prepared or formulated as a salt or derivative for some uses, including pharmaceutical and tissue or cell culture uses. As used herein, the compounds of this invention are defined to include pharmaceutically acceptable derivatives. A "pharmaceutically acceptable derivative" denotes any pharmaceutically acceptable salt, ester, thioester, amide, or salt of such ester, thioester, or amide, of a compound of this invention or any other compound which, upon administration to an animal or human patient, is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to inhibit DPP IV and/or its usefulness in treating or preventing a medical disorder. Examples of medical disorders within the scope of this aspect of the invention are given below. As

stated above, the compounds of the invention can also be part of a composition comprising one or more compounds of Formula I

The term "alkyl" refers to optionally substituted straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8, and more preferably 1-5 carbons. Exemplary unsubstituted alkyl groups include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, the various branched chain isomers thereof, such as isopropyl, t-butyl, isobutyl, isohexyl, 4,4-dimethylpentyl, 2,2,4-trimethylpentyl and the like. Substituted alkyl groups include said alkyl groups substituted by one or more substituents selected from halogen, alkoxy, cycloalkyl, hydroxy, carboxy, -CONR₆R₇, -NR₆R₇ (where R₆ and R₇ are independently hydrogen or alkyl), nitro, cyano or sulfhydryl.

The term "alkoxy" refers to an alkyl group, such as any of the above alkyl groups, linked to an oxygen atom.

The term "cycloalkyl" refers to saturated cyclic hydrocarbon groups containing 3 - 12, preferably 4 - 8, and more preferably 5 - 6 ring carbons, with cyclopentyl and cyclohexyl being most preferred.

The term "saturated mono-, di-, or tricyclic hydrocarbon" refers to cycloalkyl groups as defined in the preceding paragraph if the hydrocarbon is monocyclic. For dicyclic hydrocarbons, this definition covers saturated dicyclic groups wherein the individual rings independently consist of 4 - 12, preferably 5 - 8, and more preferably 5 - 6 carbon atoms; examples of such dicyclic groups are, without limitation, fused ring systems such as decahydro-naphthalene, octahydro-indene, bicyclo[4.2.0]octane, decahydro-benzocycloheptene, dodecahydro-benzocyclooctene, octahydro-pentalene, decahydro-azulene, decahydro-cyclopentacyclooctene, bicyclo[3.2.0]heptane, dodecahydro-heptalene, bicyclo[5.2.0]nonane, dodecahydro-cycloheptacyclooctene, and the like. For tricyclic hydrocarbons, this definition refers to saturated tricyclic groups wherein the individual rings independently consist of 4 - 12, preferably 5 - 8, and more preferably 5 - 6 carbon atoms; examples of such tricyclic groups are, without limitation, fused ring systems such as tetradecahydro-anthracene, tetradecahydro-phenanthrene, dodecahydro-phenalene, dodecahydro-acenaphthylene, dodecahydro-fluorene, dodecahydro-cyclopenta[a]indene, dodecahydro-as-indacene, dodecahydro-cyclopenta[d]naphthalene, tetradecahydro-dibenzof[a,d]cycloheptene, tetradecahydro-cyclohepta[b]naphthalene, tetradecahydro-cyclohepta[e]indene, decahydro-cyclobuta[a]indene, dodecahydro-biphenylene, and the like. "Di- and tricyclic

hydrocarbons" further refers to bridged and spirocyclic saturated groups wherein the individual rings independently consist of 4 - 12, preferably 5 - 8, and more preferably 5 - 6 carbon atoms; examples of such groups are, without limitation, adamantane, cubane, norbornane, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[3.2.1]octane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, bicyclo[3.3.2]decane, bicyclo[4.3.1]decane, bicyclo[4.4.1]undecane, bicyclo[5.4.1]dodecane, spiro[5.5]undecane, spiro[4.5]decane, and the like.

The terms "halogen" and "halo" are well-established in the chemical and pharmaceutical arts and are herein intended to have their common meaning. Preferred halo groups are fluoro-, chloro-, bromo-, and iodo-groups.

The term "aryl" refers to mono-, bi-, or tricyclic aromatic hydrocarbon groups having 6 to 14 carbon atoms in the ring portion, such as phenyl, naphthyl, tetrahydronaphthyl, biphenyl, indene, azulene, fluorene, and anthracene groups, each of which may optionally be substituted by one to four substituents such as alkyl, halo, hydroxy, alkoxy, amino, thiol, nitro, cyano, carboxy and the like.

The term "heteroaryl" refers to mono-, bi- or tricyclic unsaturated heterocyclic groups having 5-14 atoms in the ring portion, such as furan, thiophene, pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyran, pyridine, pyridazine, pyrimidine, pyrazine, triazine, indolizine, indole, isoindole, indoline, benzo[b]furan, benzo[b]thiophene, indazole, benzimidazole, benzthiazole, purine, 4H-quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1-8-naphthyridine, pteridine, carbazole, acridine, phenazine, phenothiazine, or phenoxazine, each of which may optionally be substituted by one, two, three, four, or more substituents such as alkyl, halo, hydroxy, alkoxy, amino, thiol, nitro, cyano, carboxy and the like.

The term "aralkoxy" refers to an aryl or heteroaryl group as defined above bonded to an alkoxy group.

Insofar as its preparation is not specifically mentioned or incorporated by reference herein, a compound used as a starting material for the synthesis of the compounds of this invention is known or may be prepared from known compounds, or in a known manner, or analogously to known methods, or analogously to the methods described herein, as will be appreciated by one skilled in the art. The compounds of the invention can be produced as a mixture of isomers or racemic mixtures or as optically pure compounds. Methods for separating stereoisomers known in the art can also be used

to enrich mixtures for one or more compounds. The compositions of the invention may similarly contain mixtures of stereoisomers, mixtures of one or more stereoisomers, or be enriched for one or more stereoisomers. All of these forms are specifically included in this invention and are within the scope of the claims.

5 The compounds of Formula I possess important utility as pharmaceuticals, and in the treatment of medical conditions. Examples of such medical conditions are given below. While the present invention is not bound by any theory, it is believed that the ability to bind to, and/or to inhibit DPP IV renders the compounds of this invention useful in a variety of therapeutic, diagnostic, and research applications. Thus, the compounds of
10 the invention find therapeutic application, for example, in medical conditions which can be alleviated by inhibition of DPP IV. *In vitro* techniques can be used, for example, to identify and characterize cellular components or chemical compounds that interact with DPP IV in a cell-free environment, as would be the case when a compound of Formula I is used to competitively bind to, or inhibit, DPP IV in the presence of such other chemical
15 compound or cellular component. Further, compounds of Formula I may be labeled with, or conjugated to, a suitable radioisotope, fluorescent marker, dye, or contrast agent, and in such form be utilized for determining the amount, or cellular or tissue distribution of DPP IV, in a given tissue sample, extract, homogenate, or histological specimen. In such form, the compounds of the invention may also be utilized as a diagnostic medical
20 imaging agent for the visualization of the tissue distribution of DPP IV *in vivo*, for example to detect tumors which express high levels of DPP IV.

 Another aspect of this invention provides methods for treating a medical condition in a patient in need of such treatment. Medical conditions to be treated with the compounds and compositions of this invention according to these methods include
25 neurological disorders, mental illness, diabetes, hyperglycemia, obesity, atherosclerosis, polycystic ovary syndrome, arthritis, autoimmune disorders, AIDS, osteoporosis, chronic inflammatory bowel disease, metastatic cancer, and cutaneous disorders such as psoriasis and lichen planus. The instant compounds are further useful as immunosuppressants in allograft recipients, contraceptive agents affecting sperm function, and for the treatment
30 of anorexia.

 Neurological disorders to be treated according to the methods of this invention, when present in an animal, including humans, can be neurodegenerative disorders, neuropathic disorders, neurovascular disorders, traumatic injury of the brain, spinal cord, or peripheral nervous system, demyelinating disease of the central or peripheral nervous

- system, metabolic or hereditary metabolic disorder of the central or peripheral nervous system, or toxin-induced- or nutritionally related disorder of the central or peripheral nervous system. When present in a human, a neurodegenerative disorder can be, for example, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS),
- 5 Huntington's disease, cerebellar ataxia, or multisystem atrophy including, for example, olivopontocerebellar degeneration, striatonigral degeneration, progressive supranuclear palsy, Shy-Drager syndrome, spinocerebellar degeneration and corticobasal degeneration. A demyelinating disease can be, for example, multiple sclerosis, Guillain-Barré syndrome, or chronic inflammatory demyelinating polyradiculoneuropathy. A
- 10 neurovascular disorder can be global cerebral ischemia, spinal cord ischemia, ischemic stroke, cardiogenic cerebral embolism, hemorrhagic stroke, lacunar infarction, multiple infarct syndromes including multiple infarct dementia, or any disorder resulting in ischemia or ischemia/reperfusion injury of the central nervous system. Traumatic injury of the central or peripheral nervous system can be, for example, concussion, contusion,
- 15 diffuse axonal injury, edema, and hematoma associated with craniocerebral or spinal trauma, or axonal or nerve sheath damage associated with laceration, compression, stretch, or avulsion of peripheral nerves or plexi, and further includes damage to central nervous tissue or peripheral or visceral nervous tissue caused during surgery, such as damage to the major pelvic ganglion and/or cavernous nerve caused during prostate
- 20 surgery. A neuropathic disorder can be, for example, diabetic neuropathy, uremic neuropathy, neuropathy related to therapy with drugs such as phenytoin, suramin, taxol, thalidomide, vincristine or vinblastine; or neuropathy/encephalopathy associated with infectious disease, such as, for example, encephalopathy related to HIV, rubella virus, Epstein-Barr virus, herpes simplex virus, toxoplasmosis, prion infection. A metabolic
- 25 disorder of the central nervous system can be, for example, status epilepticus, hypoglycemic coma, or Wilson's disease.

Mental illness to be treated according to the methods of this invention includes psychotic disorders such as schizophrenia or schizophreniform or schizoaffective disorder, delusional disorder, bipolar disorder or major depression when associated with

30 psychotic symptoms, and other psychotic disorders of unclear etiology, as well as psychological disorders related to the use of psychoactive substances, such as central nervous system depressants, anxiolytics, stimulants, and hallucinogens (e.g. drugs such as cocaine, alcohol, barbiturates, amphetamines, "ecstasy", heroin, morphine, LSD, cannabis, tobacco, narcotics, natural and synthetic opiates, and others). The compounds

of the invention can be used to treat not only the psychological and psychiatric symptoms associated with the use and abuse of such psychoactive substances, but are also useful in treating the addiction to, and dependency on, such substances in addicted individuals.

A compound of this invention can be administered to an animal or human patient
5 by itself or in pharmaceutical compositions where it is mixed with suitable carriers or excipients, at doses to treat or ameliorate various conditions. The compounds according to the present invention preferably have sufficient stability, potency, selectivity, solubility and availability to be safe and effective in treating diseases, injuries and other abnormal medical conditions or insults, including medical conditions of, and insults to, the central
10 nervous system, the peripheral nerves, and other organs. A therapeutically effective dose refers to that amount of the compound sufficient to effect an activity in a nerve or neuronal cell, to produce a detectable change in a cell or organism, or to treat a disorder in a human or other mammal. Non-limiting examples of therapeutically effective doses are given below. The word "treat" in its various grammatical forms as used in relation to
15 the present invention refers to preventing, curing, reversing, attenuating, alleviating, minimizing, suppressing, ameliorating or halting the deleterious effects of a disease state, disease progression, injury, wound, ischemia, disease causative agent (*e.g.*, bacteria, protozoans, parasites, fungi, viruses, viroids and/or prions), surgical procedure or other abnormal or detrimental condition (all of which are collectively referred to as
20 "disorders," as will be appreciated by the person of skill in the art). A "therapeutically effective amount" of a compound according to the invention is an amount that can achieve effective treatment, and such amounts can be determined in accordance with the present teachings by one skilled in the art.

The methods of the present invention comprise (i.) administration of a compound
25 of Formula I, where the compound is itself therapeutically active in the treatment of the targeted medical condition, or (ii.) administration of a prodrug of a compound of Formula I, wherein such prodrug is any compound which is capable of undergoing metabolic conversion to a compound of Formula I following administration, or (iii.) administration of a compound of Formula I where the compound is capable of undergoing metabolic
30 conversion to a metabolite following administration, and where the metabolite is therapeutically active in the treatment of the targeted medical condition, or (iv.) administration of a metabolite of a compound of Formula I, where the metabolite is therapeutically active in the treatment of the targeted medical condition. Thus, the use of a compound of Formula I in the methods of the present invention explicitly includes not

only the use of the compound itself, but also the modifications ii, iii, and iv discussed in this paragraph, and all such modifications are explicitly intended to be within the scope of the following claims.

Therapeutically effective doses may be administered alone or as adjunctive
5 therapy in combination with other treatments. Techniques for the formulation and administration of the compounds of the instant application may, for example, be found in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 18th edition (1990), and subsequent editions thereof.

Suitable routes of administration may, for example, include oral, rectal,
10 transmucosal, buccal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, and optionally in a depot or sustained release formulation. Furthermore, one may administer the agent of the present invention in a targeted drug delivery system, for example in a
15 liposome coated with an antibody. The liposomes will be targeted to and taken up selectively by cells expressing the appropriate antigen.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical
20 compositions for use in accordance with the present invention thus may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations, which can thus be used pharmaceutically.

For injection, the compounds of the invention may be formulated in aqueous
25 solutions, preferably in physiologically compatible buffers, such as Hank's solution, Ringer's solution, or physiological saline buffer. For transmucosal or buccal administration, penetrants appropriate to the barrier to be permeated may be used in the formulation. Such penetrants are known in the art. Optionally, lyophilizates comprising one or more compounds of Formula I may be reconstituted in sterile saline, water, or
30 buffer prior to injection.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers, well known to those in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, quick-dissolving preparations, gels, syrups, slurries, suspensions

and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use of the compounds of this invention can be obtained by employing a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP).

In general, the pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate or a number of others disintegrants (see, for example, *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 18th edition (1990), and subsequent editions thereof).

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, pressurized air, or other suitable gas or mixture. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or

agents, which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as
5 suppositories, e.g., containing conventional suppository bases such as cocoa butter or other glycerides. In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with
10 suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The compounds of the invention may further be formulated in pharmaceutical or cosmetic compositions for topical application to the skin in the form of an aqueous,
15 alcoholic, aqueous/alcoholic or oily solution, or of a dispersion of the lotion or serum type, of an emulsion having a liquid or semi-liquid consistency of the milk type, obtained by dispersion of a fatty phase in an aqueous phase (O/W) or vice versa (W/O), or of a suspension or of an emulsion with a soft consistency of the aqueous or anhydrous gel, foam or cream type, or, alternatively, of microcapsules or microparticles, or of a vesicular
20 dispersion of ionic and/or nonionic type, or may further be administered in the form of an aerosol composition comprising a pressurized propellant agent. The compounds of the invention, for use in the treatment of a cutaneous disorder such as, for example, psoriasis or lichen planus, can also be formulated into various compositions for hair care and, in particular, shampoos, hair-setting lotions, treating lotions, styling creams or gels, dye
25 compositions (in particular oxidation dyes), optionally in the form of color-enhancing shampoos, hair-restructuring lotions, permanent-wave compositions, and the like.

Pharmaceutical or cosmetic compositions comprising compounds of the invention can also contain additives and adjuvants which are conventional in the cosmetics field, such as gelling agents, preservatives, antioxidants, solvents, fragrances, fillers, screening
30 agents, odor absorbers and colorants. The amounts of these different additives and adjuvants are those typically employed in the cosmetics field and range, for example, from 0.01% to 20% of the total weight of the composition, preferably 0.1% to 10%, and more preferably 0.5% to 5%. In addition to one or several compounds of the invention, compositions for topical application may further contain agents known in the art to

promote hair growth or to prevent or retard hair loss, such as, without limitation, tocopherol nicotinate, benzyl nicotinate or 2,4-diamino-6-piperidinopyrimidine 3-oxide, or may contain other active agents such as antibacterial agents, antiparasitic agents, antifungal agents, antiviral agents, anti-inflammatory agents, antipruriginous agents, anaesthetic agents, keratolytic agents, antiseborrhoeic agents, antidandruff agents, or antiacne agents. The cosmetic or pharmaceutical compositions according to the invention can be topically applied onto the affected areas of the scalp and skin of an individual and optionally maintained in contact for a number of hours and optionally rinsed. It is possible, for example, to apply the composition containing an effective amount of at least one compound of the invention in the evening, to retain the composition in contact overnight and optionally to shampoo in the morning. These applications can be repeated daily for one or a number of months, depending on the particular individuals involved.

Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for stabilization may be employed.

The compounds of this invention may be administered in conjunction with, or formulated in pharmaceutical compositions together with, one or several additional therapeutic agents. Such additional therapeutic agents are themselves known in the art, and the specific agent employed together with the compounds of Formula I in this embodiment of the invention depend on the medical condition to be treated. Medical conditions wherein the compounds of Formula I are useful as therapeutic agents include diabetes, hyperglycemia, impaired glucose homeostasis, impaired glucose tolerance, infertility, polycystic ovary syndrome, growth disorders, frailty, arthritis, allograft rejection in transplantation, autoimmune diseases (such as scleroderma and multiple sclerosis), various immunomodulatory diseases (such as lupus erythematosus or psoriasis), AIDS, intestinal diseases (such as necrotizing enteritis, microvillus inclusion disease or celiac disease), inflammatory bowel syndrome, chemotherapy-induced intestinal mucosal atrophy or injury, osteoporosis, Syndrome X, dysmetabolic syndrome,

diabetic complications, hyperinsulinemia, obesity, atherosclerosis and related diseases, as well as inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), neurodegenerative disorders, and mental illness. The instant compounds are further useful as immunosuppressants in allograft recipients, contraceptive agents affecting sperm

5 function, and for the treatment of anorexia. It follows that additional therapeutic agents to be used in combination with the compounds of this invention are selected from such agents known in the art to possess therapeutic utility in the medical condition to be treated. In the treatment of diabetes, for example, compounds of Formula I may be used

10 in combination with one or more other types of antidiabetic agents which may be administered by any of the herein described routes in the same dosage form, or in a separate dosage form. Such other types of antidiabetic agents which may be used in combination with the compounds of this invention are themselves known in the art, and include, for example, biguanides, sulfonyl ureas such as glyburide, glucosidase inhibitors, thiazolidinediones such as troglitazone (Rezulin ®), glycogen phosphorylase inhibitors,

15 and insulin. In the treatment of inflammatory disorders, for example, compounds of Formula I may be used in combination with one or several agents which themselves have therapeutic utility in that condition, such as aspirin, indomethacin, ibuprofen, ketoprofen, naproxen sodium, celecoxib (Celebrex ®), or rofecoxib (Vioxx ®).

In the treatment of mental illness, such as, for example, a psychotic disorder like

20 schizophrenia, the antipsychotic compounds of Formula I may be administered in conjunction with one or several other antipsychotic agents such as neuroleptics from the butyrophenone or phenothiazine classes. Neuroleptic drugs are well-known in the art and include, for example, clozapine, olanzapine, risperidone, sertindole, quetiapine, ziprasadone, amisulpride, acetophenazine, chlorpromazine, chlorprothixene,

25 fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, piperacetazine, trifluoperazine, triflupromazine, thioridazine, and thiothixene.

Toxicity and therapeutic efficacy of the compounds or compositions can be determined by standard pharmaceutical, pharmacological, and toxicological procedures in cell cultures or experimental animals. For example, numerous methods for determining

30 the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population) exist. The dose ratio between toxic and therapeutic effects is the therapeutic index, which can be expressed as the ratio between LD₅₀ and ED₅₀. Compounds and compositions exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays or animal studies can be used in formulating a

range of dosages for use in humans, as has long been established in the art [*see, e.g., Fingl et al., in The Pharmacological Basis of Therapeutics, Ch. 1 p. 1 (1975)*].

The compounds of the present invention may be administered by a single daily dose, multiple discrete doses, for example 3 times per day, or by continuous infusion.

5 Dose levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient are useful in the treatment of the above conditions, with preferred levels being about 0.1 mg to about 4,000 mg, and 1 mg to about 1000 mg. The specific dose level, and thus the therapeutically-effective amount, for any particular patient will vary depending upon a variety of factors, including the activity of the specific compound employed and its
10 bioavailability at the site of drug action; the age, body weight, general health, sex and diet of the patient; the time of administration; the rate of excretion; drug combination; the severity of the particular disease being treated; and the form of administration. Typically, *in vitro* dosage-effect results provide useful guidance on the proper doses for patient administration. Studies in animal models also are helpful. The considerations for
15 determining the proper dose levels are available to the skilled person.

Suitable compounds of this invention can be administered in lyophilized form, as discussed above. In this case, 1 to 1000 mg, preferably 20 – 500 mg, of a compound of the present invention may be lyophilized in individual vials, together with a carrier and a buffer, such as mannitol and sodium phosphate. The compound may be reconstituted in:
20 the vials with bacteriostatic water before administration.

In treating a neurodegenerative disorder, for example, the compounds of the present invention are preferably administered orally, rectally, or parenterally 1 to 6 times daily, and may follow an initial bolus dose of higher concentration. In treating a cutaneous disorder, such as psoriasis or lichen planus, for example, the compounds of the
25 present invention are preferably administered topically or orally one to four times daily.

For the compounds, methods, and uses of the present invention, any administration regimen regulating the timing and sequence of drug delivery can be used and repeated as necessary to effect treatment. Such regimen may include pretreatment and/or co-administration with additional therapeutic agents.

30 The following description should not be taken as a limitation on the scope of the invention, and all embodiments and examples given are merely illustrative of the invention. Additional aspects of the invention can be devised by reference to this disclosure as a whole in combination with the references cited and listed throughout and at the end of the specification and the knowledge of one skilled in the art. All of the

references cited and listed can be relied on, in their entirety, to allow one to make and use these additional aspects of the invention.

Synthetic pathways to the compounds of the invention

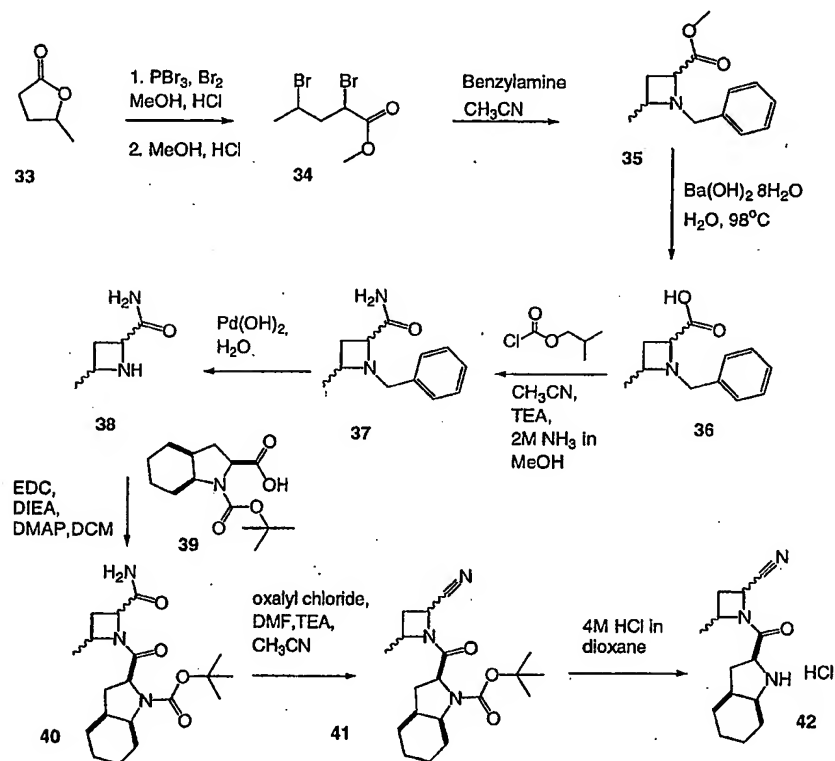
5

Synthesis of 4-Methyl-1-(octahydro-indole-2-carbonyl)-azetidine-2-carbonitrile hydrochloride, compound (42):

The synthesis of the title compound is conducted according to the procedure outlined in Scheme I, below.

10

Scheme I



2,4-Dibromo-pentanoic acid methyl ester (34): A solution of 5-methyl-dihydro-furan-2-one (33, 48.68 g, 0.486 mol) and phosphorous tribromide (2.8 g, 0.0104 moles) was

15 heated to 100 °C. Bromine (27.32 mL, 0.0548 mol) was added dropwise while maintaining the temperature at 100 °C. Bromine uptake was monitored visually, i.e., once orange coloration of the solution disappeared, additional bromine was added. When bromine consumption was stopped (i.e., reaction solution remained dark-orange despite

further addition of bromine), an additional amount of phosphorous tribromide was added (4 equivalents total). The reaction solution was cooled to 0 °C, and methanol (240 mL) was added. The solution was stirred for a short time, and a stream of anhydrous HCl was passed through the reaction mixture for 5h. HCl delivery was discontinued, and the reaction mixture was stirred overnight. Solvents were removed under vacuum, and the residue was partitioned between diethyl ether (50 ml) and NaHCO₃ (3% aq. solution, 25 ml). The aqueous layer was then extracted with diethyl ether (3x50 ml), dried over MgSO₄, filtered, concentrated, and purified by column chromatography (silica gel, eluent: 4:1 hexane:EtOAc). Pale pink oil; yield 99.09 g (74.9%).

10

1-Benzyl-4-methyl-azetidine-2-carboxylic acid methyl ester (35): To a stirred solution of 2,4-dibromo-pentanoic acid methyl ester (34, 27.17 g, 0.1 mol) in acetonitrile (300mL) was added benzylamine (32.74 mL, 0.3 mol). The solution was stirred and refluxed overnight. The resulting mixture was cooled to room temperature, and diluted with diethyl ether (150 mL). Solid precipitates were filtered. The filtrate was concentrated in vacuum, and the resulting residue was partitioned between EtOAc (100 mL) and water (50 mL). The aqueous layer was separated and additionally extracted with EtOAc (3x50 mL). Combined organic layers were washed with brine, separated, dried over Na₂SO₄, filtered, concentrated, and purified by column chromatography (silica gel, eluent: 4:1 hexane:EtOAc) to give the product as a light oil; yield 6.42 g (29%).

20

1-Benzyl-4-methyl-azetidine-2-carboxylic acid (36): A mixture of 1-benzyl-4-methyl-azetidine-2-carboxylic acid methyl ester (35, 5.03 g, 0.023 mol) and Ba(OH)₂ 8H₂O (4.52 g, 0.014 mol) in water (70.0 mL) was refluxed for 15 min. While the solution was still hot, a stream of anhydrous CO₂ was passed through the reaction solution. White precipitate started to form immediately. Addition of CO₂ was discontinued when no further precipitation was observed. The solids were then filtered, and the filtrate concentrated in vacuum to give a white solid; yield 4.36 g (92%).

25

1-Benzyl-4-methyl-azetidine-2-carboxylic acid amide (37): To a cooled (0 °C) mixture of 1-benzyl-4-methyl-azetidine-2-carboxylic acid (36, 4.36 g, 0.021 mol) and acetonitrile (200 mL) was added triethylamine (4.03 mL, 0.029 mol) dropwise. After addition, the solution was briefly stirred, and isobutyl chloroformate (4.13 mL, 0.032 mol) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred for 1 h, and a

30

solution of NH_3 in MeOH (2M, 72.5 mL, 2.46g, 0.145 mol) was added. A yellowish suspension formed under stirring for 1.5 h at 0 °C. The yellowish suspension was partitioned between EtOAc (50 mL) and water (20 mL), the organic layer was separated, and the aqueous layer was additionally extracted with EtOAc (3x50 mL). Combined
5 organic layers were washed with brine, separated, dried over Na_2SO_4 , filtered, concentrated, and purified by column chromatography (silica gel, eluent: EtOAc) to give the product as a waxy solid; yield 0.94 g (22%).

4-Methyl-azetidine-2-carboxylic acid amide (38): To a solution of 1-benzyl-4-methyl-azetidine-2-carboxylic acid amide (37, 0.94 g, 0.0046 mol), in MeOH (100 mL) was
10 added $\text{Pd}(\text{OH})_2$ (0.95 g). The whole was transferred into a Parr flask, and subjected to hydrogenation with H_2 (applied pressure of 55 p.s.i) on a Parr apparatus. After 3 h, solids were filtered and the reaction solution was concentrated to give a white solid; yield 0.52 g (99%).

15 2-(2-Carbamoyl-4-azetidine-1-carbonyl)-octahydro-indole-1-carboxylic acid tert-butyl ester (40): To a solution of 4-methyl-azetidine-2-carboxylic acid amide (38, 0.29 g, 0.0025 mol) in dichloromethane (10 mL), cooled to 0 °C, was added diisopropylethylamine (0.65 g, 0.0038 mol), followed by addition of N,N-dimethylpyridine (20 mg). The solution was stirred for 30 minutes, and octahydro-indole-
20 1,2-dicarboxylic acid 1-tert-butyl ester (39, 0.82 g, 0.0031 mol) was added, followed by addition of EDC (0.59 g, 0.0031 mol). The reaction mixture was stirred overnight. Solvents were removed under reduced pressure, and the residue was partitioned between EtOAc (50 mL) and water (20 mL). The aqueous layer was separated and additionally
25 extracted with EtOAc (3x50 mL). Combined organic layers were washed with brine, separated, dried over Na_2SO_4 , filtered, concentrated, and purified by column chromatography (silica gel, eluent: 99:1 EtOAc:tetrahydrofuran) to give the product as a glassy solid; yield 0.23 g (25%). ^1H NMR (CDCl_3) δ , ppm: 1.24 - 1.28 (m, 6H), 1.40-1.54 (m, 11H), 1.42 (s, 3H), 1.58-1.74 (m, 3H), 2.27-2.35 (m, 2H), 4.36-4.84 (m, 3H).

30 2-(2-cyano-4-methyl-azetidine-1-carbonyl)-octahydro-indole-1-carboxylic acid tert-butyl ester (41): To a cooled (0 °C) mixture of DMF (0.16 mL) and acetonitrile (2.0 mL) was added oxalyl chloride (0.18 mL) dropwise. The suspension formed was stirred at 0 °C for 1 h. A solution of 2-(2-carbamoyl-4-azetidine-1-carbonyl)-octahydro-indole-1-

carboxylic acid *tert*-butyl ester (40) (0.59 g, 0.0017 mol) in acetonitrile (2.0 mL) was added dropwise, and stirring was continued for 1h. The reaction was quenched with triethylamine (0.52 mL), and after 10 min the resulting mixture was partitioned between EtOAc (30 mL) and water (20 mL). The organic layer was separated and the aqueous layer extracted with of EtOAc (3x10 mL). The combined organic layers were washed with brine, separated, dried over Na₂SO₄, filtered, concentrated, and purified by column chromatography (silica gel, eluent: EtOAc) to give the product as a white solid; yield 0.44 g (72%). ¹H NMR (CDCl₃) δ, ppm: 1.24-1.28 (m, 6H), 1.40-1.54 (m, 11H), 1.42 (s, 3H), 1.58-1.74 (m, 3H), 2.27-2.35 (m, 2H), 4.36-4.84 (m, 3H).

10

4-Methyl-1-(octahydro-indole-2-carbonyl)-azetidine-2-carbonitrile hydrochloride (42): A mixture of 2-(2-cyano-4-methyl-azetidine-1-carbonyl)-octahydro-indole-1-carboxylic acid *tert*-butyl ester (41, 0.44 g, 0.0013 mol) and a solution of HCl in dioxane (4M, 3.28 mL) was stirred at room temperature for 1 h. Solvent was removed in vacuum, and the resulting solid was washed with diethyl ether (3x10 mL). The title compound was collected by filtration of the last wash to afford a white hygroscopic solid; yield 0.32 g (87%). ¹H NMR (CDCl₃) δ, ppm: 1.09-1.52 (m, 11H), 1.63-1.94 (m, 3H), 2.09-2.31 (m, 2H), 2.62-2.83 (m, 1H), 3.57-3.60 (m, 1H), 4.21-4.22 (m, 1H), 4.50 (bm, 1H). Anal. calcd. for C₁₄H₂₁N₃O (1.2 HCl)(0.5 Et₂O): C, 58.24; H, 8.32; N, 12.73. Found: C, 58.23; H, 8.04; N, 12.42.

20

Synthesis of 1-(2-Amino-3-methyl-butyryl)-4-methyl-azetidine-2-carbonitrile hydrochloride, (compound 46):

The synthesis of the title compound was conducted according to Scheme II, below.

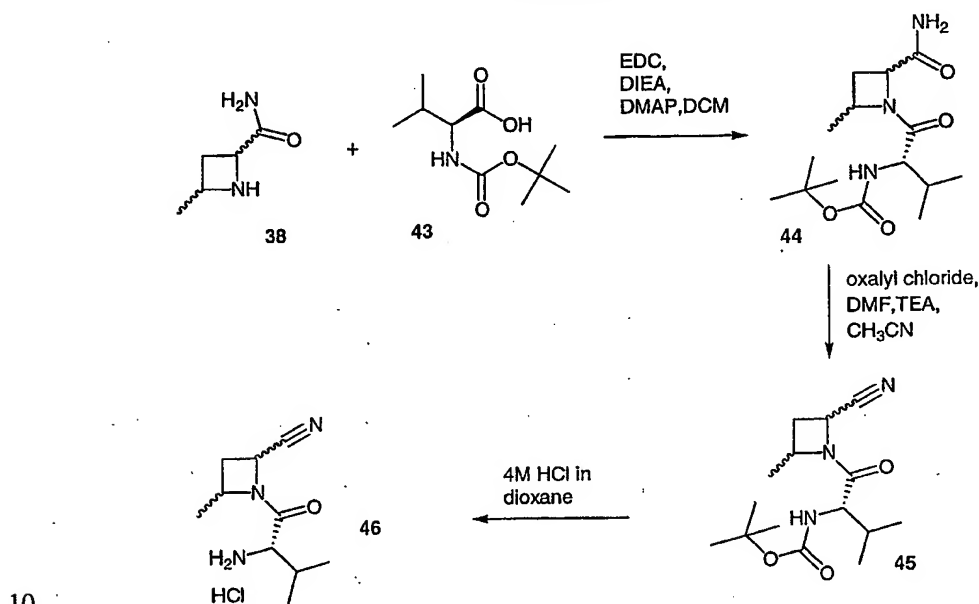
25

[1-(2-Carbamoyl-4-methyl-azetidine-1-carbonyl)-2-methyl-propyl]-carbamic acid *tert*-butyl ester (44): To a solution of 4-methyl-azetidine-2-carboxylic acid amide (38, 0.13 g, 0.0011 mol; for preparation see Scheme I, above), in dichloromethane (10 mL), cooled to 0 °C, was added diisopropylethylamine (0.65 g, 0.004 mol), followed by addition of N,N-dimethylpyridine (20 mg). The whole was stirred for 30 minutes, and 2-*tert*-butoxycarbonylamino-3-methyl-butyric acid (43, 0.28 g, 0.0016 mol) was added, followed by addition of EDC (0.25 g, 0.0013 mol). The reaction mixture was stirred overnight. Solvents were removed under reduced pressure, and the residue was partitioned between EtOAc (10 mL) and water (10 mL). The aqueous layer was

30

separated and additionally extracted with EtOAc (3x50 mL). Combined organic layers were washed with brine, separated, dried over Na₂SO₄, filtered, concentrated and purified by column chromatography (silica gel, eluent: 99:1 EtOAc:tetrahydro-furan) to give the product as a glassy solid; yield 0.11 g (32%). ¹H NMR (CDCl₃) δ, ppm: 0.93-1.03 (m, 6H), 1.43 (s, 9H), 1.52 (d, 3H), 1.56 (d, 3H), 2.00-2.29 (m, 2H), 2.61-2.66 (m, 1H), 3.88-4.10 (m, 1H), 4.70-4.91 (m, 1H), 5.50-5.54 (m, 1H). Anal. calcd. for C₁₅H₂₇N₃O₄ (0.5 EtOAc): C, 57.49; H, 8.68; N, 13.41. Found: C, 57.12; H, 8.74; N, 11.76.

Scheme II



[1-(2-Cyano-4-methyl-azetidine-1-carbonyl)-2-methyl-propyl]-carbamamic acid *tert*-butyl ester (45): To a cooled (0 °C) solution of DMF (0.05 mL) and acetonitrile (1 mL) was added oxalyl chloride (0.041 mL) dropwise. The formed suspension was stirred at 0 °C for 1 h. A solution of [1-(2-carbamoyl-4-methyl-azetidine-1-carbonyl)-2-methyl-propyl]-carbamamic acid *tert*-butyl ester (44, 0.11 g, 0.0004 mol) in acetonitrile (1 mL) was added dropwise, and stirring was continued for 1 h. The reaction was quenched with triethylamine (0.012 mL), and after 10 min the resulting mixture was partitioned between EtOAc (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was additionally extracted with EtOAc (3x10 mL). Combined organic layers were washed with brine, separated, dried over Na₂SO₄, filtered, concentrated, and purified by column chromatography (silica gel, eluent: EtOAc) to give the product as a white solid;

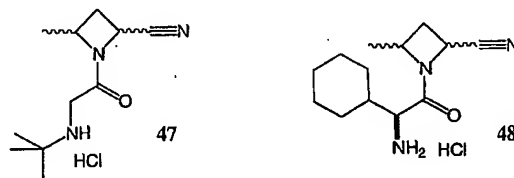
15

20

yield 0.09 g (81%). ^1H NMR (CDCl_3) δ , ppm: 1.24-1.28 (m, 6H), 1.40-1.54 (m, 11H), 1.42 (s, 3H), 1.58 - 1.74 (m, 3H), 2.27 - 2.35 (m, 2H), 4.36 - 4.84 (m, 3H).

1-(2-Amino-3-methyl-butyl)-4-methyl-azetidine-2-carbonitrile hydrochloride (46): A mixture of [1-(2-cyano-4-methyl-azetidine-1-carbonyl)-2-methyl-propyl]-carbamic acid *tert*-butyl ester (45, 0.09 g, 0.0003 mol) and HCl solution in dioxane (4M, 0.75 mL) was stirred at room temperature for 1 h. Solvent was removed in vacuum, and the resulting solid was washed with diethyl ether (3x4 mL). The title compound was collected by filtration of the last wash to afford white hygroscopic solid; yield 0.06 g (99%). ^1H NMR (CDCl_3) δ , ppm: 1.05-1.21 (m, 6H), 1.63-1.66 (m, 3H), 1.71-1.74 (m, 3H), 2.32-2.57 (m, 1H), 3.04-3.17 (m, 2H), 3.83-4.11 (m, 1H), 5.03-5.23 (m, 1H). Anal. calcd. for $\text{C}_{10}\text{H}_{17}\text{N}_3\text{O}(1.55 \text{ HCl})(0.25 \text{ Et}_2\text{O})$: C, 48.88; H, 7.85; N, 15.55. Found C, 48.85; H, 7.84; N, 15.75.

The following compounds were also prepared from compound 38 in a manner similar to that depicted in Schemes I and II, above:



1-(2-*tert*-Butylamino-acetyl)-4-methyl-azetidine-2-carbonitrile hydrochloride (47): white hygroscopic solid; yield 0.073 g (99%). ^1H NMR (CDCl_3) δ , ppm: 1.16 (s, 9 H), 1.26-1.28 (d, $J = 6.3$ Hz, 3H), 1.34-1.36 (d, $J = 6.3$ Hz, 3H), 2.10-2.60 (m, 1H), 2.62-2.71 (m, 1H), 3.32-3.70 (m, 2H), 4.44-4.73 (m, 1H), 4.75-4.87 (m, 1H). Anal. calcd. for $\text{C}_{11}\text{H}_{19}\text{N}_3\text{O}(1.6 \text{ HCl})(0.45 \text{ Et}_2\text{O})$: C, 51.08; H, 8.41; N, 13.96. Found: C, 51.19; H, 8.48; N, 13.99.

1-(2-Amino-2-cyclohexyl-acetyl)-4-methyl-azetidine-2-carbonitrile hydrochloride (48): white hygroscopic solid; yield 0.020 g (99%). ^1H NMR (CDCl_3) δ , ppm: 0.96-1.09 (m, 4H), 1.36-1.77 (m, 12 H), 2.20-2.26 (m, 1H), 2.87-2.91 (m, 1H), 3.68-3.72 (m, 1H), 4.61-

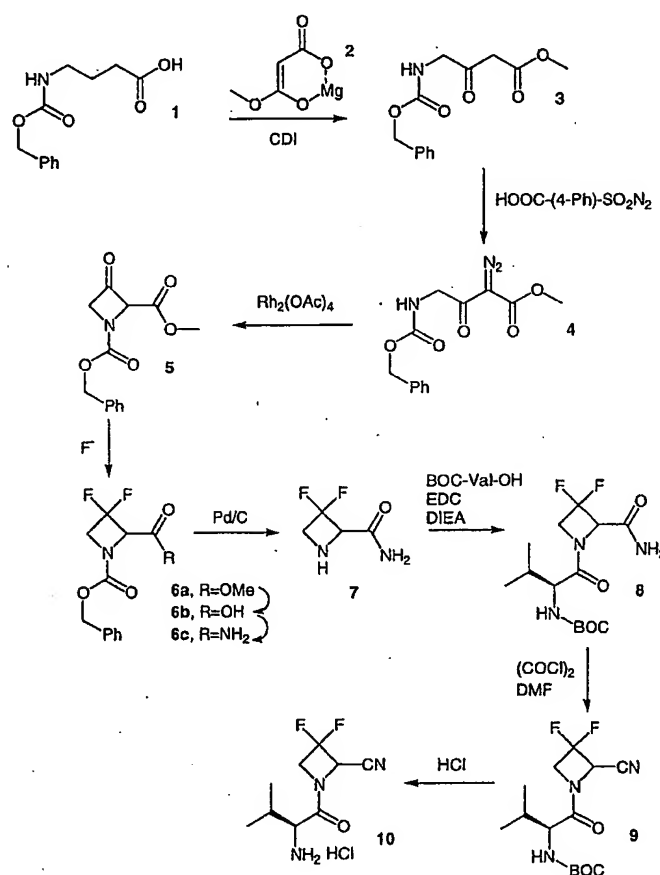
4.65 (m, 1H), 4.86-4.91 (m, 1H). Anal. calcd. for $C_{13}H_{21}N_3O(1.25 \text{ HCl})(0.35 \text{ Et}_2\text{O})$: C, 56.37; H, 8.46; N, 13.69. Found: C, 56.13; H, 8.24; N, 13.43.

Synthesis of 1-(2-Amino-3-methyl-butyryl)-3,3-difluoroazetidine-2-carbonitrile

5 Hydrochloride (10, Scheme III):

The title compound is prepared according to the procedures of Scheme III, below.

Scheme III



10

4-Benzyloxycarbonylamino-3-oxobutyric acid methyl ester (3, Scheme III): To solution of 4-(CBZ-amino)butyric acid (1, Scheme III, 2.37 g, 10 mmol) in dry THF (50 mL) is added 1,1-carbonyldiimidazole (120 mol.%), and the whole is stirred at r.t. for 6 h (Solution A). In a separate flask, to a stirred and chilled (0 °C) solution of hydrogen methyl malonate (1.77 g, 15 mmol) in dry THF (25 mL) is added a solution of *iso*-

propylmagnesium chloride in hexanes (1M solution, 30 mmol); the whole is stirred at 0 °C for 45 min and then at r.t. for 1 h, thus forming a chelate **2** (Scheme III). To this solution is added Solution A (*see above*) at 0 °C under stirring. The gummy precipitate initially formed is allowed to warm up to r.t. within 1 h, and stirring is continued for
5 another 3 h. The reaction mixture is poured into ice-water (500 g), containing a solution of NaHSO₄ (10%, 50 mL). Organics are extracted with EtOAc (3x100 mL), washed with NaHCO₃ (sat., 50 mL), brine (50 mL), separated, dried over Na₂SO₄, filtered and solvents are removed in vacuum to give keto-ester **3** of sufficient purity for a further reaction as yellowish wax; expected yield 1.82 g (69%).

10

4-Benzylloxycarbonylamino-2-diazo-3-oxobutyric acid methyl ester (**4**, Scheme III): To a stirred solution of compound **3** (1.75 g, 6.6 mmol) in acetonitrile (75 mL) is added 4-carboxybenzenesulfonazide (1.50 g, 6.6 mmol), and the mixture is chilled to 0 °C. Diisopropylethylamine (3.50 mL, 20 mmol) is added in one portion, and the whole is
15 allowed to warm up to r.t. under stirring for 2 h. Organics are extracted with ether (3x75 mL), and dichloromethane (2x50 mL). Combined organic extracts are washed with an aqueous solution of NaOH (1M, 100 mL), separated, dried over MgSO₄, filtered, and solvents are evaporated to give the diazo-compound as a yellowish solid; yield 1.30 g. Crude product is purified by column chromatography (silics gel; eluent - hexanes:EtOAc,
20 1:1) to afford pure product as a white solid; expected yield 1.10 g (57%).

1-Benzylloxycarbonyl-2-methoxycarbonyl 3-oxoazetidine (**5**, Scheme III): To a stirred solution of compound **4** (1.00 g, 3.43 mmol) in benzene (50 mL) is added Rh₂(OAc)₄ (0.6 mol.%), and the whole is immediately immersed into a pre-heated 80-90 °C oil bath.
25 Stirring is continued until TLC shows complete consumption of starting material. The reaction mixture is cooled to r.t. and quickly filtered through a short column with neutralized (pH 7, SiliCycle (TM)) silica gel. Solvent is evaporated in vacuum to afford crude product of sufficient purity as yellow oil, expected yield 0.46 g (51%).

30 1-Benzylloxycarbonyl-2-methoxycarbonyl 3,3-difluoroazetidine (**6a**, Scheme III): A solution of compound **5** (0.45 g, 1.7 mmol) and DAST (0.68 mL, 5.2 mmol) in dry dichloromethane (25 mL) is stirred at r.t. for 3 days. Solvent is removed in vacuum, and the resulting pale-yellow oil is purified by column chromatography (silica gel, eluent -

hexanes:EtOAc 2:1) to afford a pure product; yellowish light oil, expected yield 0.36 g (75%).

5 1-Benzyloxycarbonyl-3,3-difluoroazetidine-2-carboxylic acid (6b): This compound is prepared by conventional hydrolysis of the ester **6a** with aqueous NaOH in methanol at room temperature over the course of 3 h. Yellowish-white solid; expected yield 88%.

10 1-benzyloxycarbonyl-2-3,3-difluoroazetidine-2-carboxamide (6c): This compound is prepared from the acid **6b** by reacting it with *i*-BuOCOC₂H₅ to form the mixed anhydride, which is then quenched with excess ammonia in methanol. White solid; expected yield 71%.

3,3-difluoroazetidine-2-carboxamide (7): This compound is prepared from the amide **6c** by hydrogenation on Pd/C at 50 psi for 2 h. White solid; expected yield 99%.

15

1-[2-(*t*-Butyloxycarbonylamino)-3-methyl-butyl]-3,3-difluoroazetidine-2-carboxamide (8, Scheme III): To a solution of 3,3-difluoroazetidine-2-carboxamide (**7**, 0.35 g, 2.6 mmol) in dichloromethane (20 mL), cooled to 0 °C, is added diisopropylethylamine (0.65 g, 3.8 mmol), followed by addition of N,N-dimethylpyridine (0.03 g). The solution is stirred for 15 minutes, and BOC-Val-OH (0.65 g, 3.0 mmol) is added, followed by addition of EDC (0.58 g, 3.0 mmol). The reaction mixture is allowed to stir overnight. Solvents are removed under reduced pressure, and the residue is partitioned between EtOAc (50 mL) and water (20 mL). The aqueous layer is separated and additionally extracted with EtOAc (3x50 mL). Combined organic extracts are washed with brine (50 mL), separated, dried over Na₂SO₄, filtered, concentrated, and purified by column chromatography (silica gel, eluent: 99:1 EtOAc:tetrahydrofuran) to give the product as white solid; expected yield 0.56 g (64%).

25
30 1-[2-(*t*-Butoxycarbonylamino)-3-methyl-butyl]-3,3-difluoroazetidine-2-carbonitrile (9, Scheme III): To a chilled (0 °C) mixture of DMF (0.16 mL, 2.0 mmol) and acetonitrile (10 mL) is added oxalyl chloride (0.18 mL, 2.0 mmol) dropwise. The formed suspension is stirred at 0 °C for 1 h. A solution of compound **8** (0.55 g, 1.6 mmol) in acetonitrile (5 mL) is then added dropwise, and stirring is continued for 1h. The reaction is quenched with triethylamine (0.55 mL), and after 10 min the resulting mixture is partitioned

between EtOAc (30 mL) and water (20 mL). The organic layer is separated, and the aqueous layer is additionally extracted with EtOAc (3x10 mL). The combined organic layers are washed with brine (50 mL), separated, dried over Na₂SO₄, filtered, concentrated, and purified by column chromatography (silica gel, eluent: hexanes:EtOAc, 1:4) to give the product as white solid; expected yield 0.45 g (71%).

1-(2-Amino-3-methyl-butyryl)-3,3-difluoroazetidine-2-carbonitrile Hydrochloride (10, Scheme III): A mixture of compound 9 (0.43 g, 1.4 mmol) and a solution of HCl in dioxane (4M, 5 mL) is stirred at r.t. for 1 h. Solvent is removed in vacuum, and the resulting solid is washed with diethyl ether (3x10 mL). The product is collected by filtration of the last wash to afford a white hygroscopic solid; expected yield 0.35 g (89%).

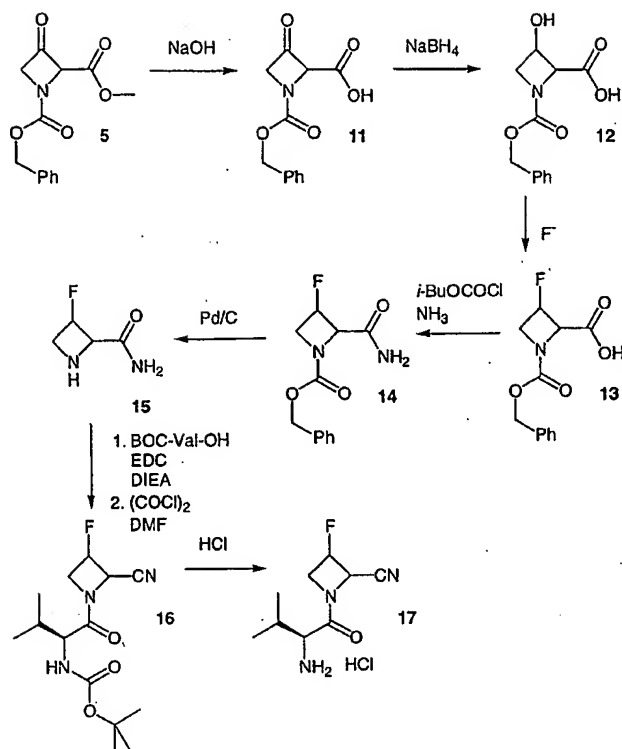
Synthesis of 1-(2-Amino-3-methyl-butyryl)-3-fluoroazetidine-2-carbonitrile Hydrochloride (17, Scheme IV):

The title compound is prepared according to the procedures outlined in Scheme IV, below.

1-Benzyloxycarbonyl-3-oxoazetidine 2-carboxylic acid (11, Scheme IV): To a stirred solution of compound 5 (see Scheme III, above; 2.00 g, 7.6 mmol) in methanol (50 mL) is added a solution of NaOH (0.30 g, 7.6 mmol) in water (30 mL) at r.t. After stirring for 2 h, a yellowish solution is extracted twice with diethyl ether (50 mL); the aqueous layer is separated and acidified with HCl (0.1 N aq.) to pH 2. After standing for 2 h, the slurry is filtered to give the acid 11 of sufficient purity for further reaction; white solid, expected yield 1.74 g (94%).

1-Benzyloxycarbonyl-3-hydroxyazetidine 2-carboxylic acid (12, Scheme IV): To a stirred and chilled at 0 °C solution of the acid 11 (1.70 g, 6.8 mmol) in ethanol (75 mL) is added NaBH₄ (0.38 g, 10 mmol). The whole is stirred for 3 h. The reaction mixture is quenched with a saturated aqueous solution of citric acid and extracted with EtOAc (8x50 mL). Organic extracts are combined, dried over MgSO₄, filtered, and concentrated in vacuum to give the product as white solid; expected yield 0.95 g (56%).

Scheme IV



- 5 1-Benzyloxycarbonyl-3-fluoroazetidine 2-carboxylic acid (13): To a stirred and chilled (0 °C) solution of compound 12 (0.90 g, 3.6 mmol) in dry dichloromethane (25 mL) is added a solution of DAST (0.74 mL, 7.2 mmol) in dry dichloromethane (7 mL) dropwise. After addition, the whole is stirred at r.t. for 1h. Solvent is removed in vacuum, and the resulting brown-yellow oil carefully partitioned between EtOAc (50 mL) and aqueous
- 10 NaOH (0.1N, 50 mL). The organic layer is separated, dried over MgSO₄, filtered, and concentrated in vacuum to give a brown oil, which is purified by column chromatography (silica gel, eluent – THF:EtOAc 1:3) to afford the pure product as a pale-yellow wax, expected yield 0.67 g (73%).
- 15 1-Benzyloxycarbonyl-3-fluoroazetidine 2-carboxamide (14), 3-fluoroazetidine-2-carboxamide (15), 1-[2-(t-butoxycarbonylamino)-3-methyl-butyl]-3-fluoroazetidine-2-carbonitrile (16), and 1-(2-amino-3-methyl-butyl)-3-fluoroazetidine-2-carbonitrile hydrochloride (17): These compounds are prepared according to the procedures given above for the corresponding difluoro-analogs. Cpd. 14: white solid; expected yield 58%.

Cpd. 15: white solid; expected yield 97%. Cpd. 16: Light-pink solid; expected yield 49%.

Cpd. 17: white hygroscopic solid; expected yield 49%.

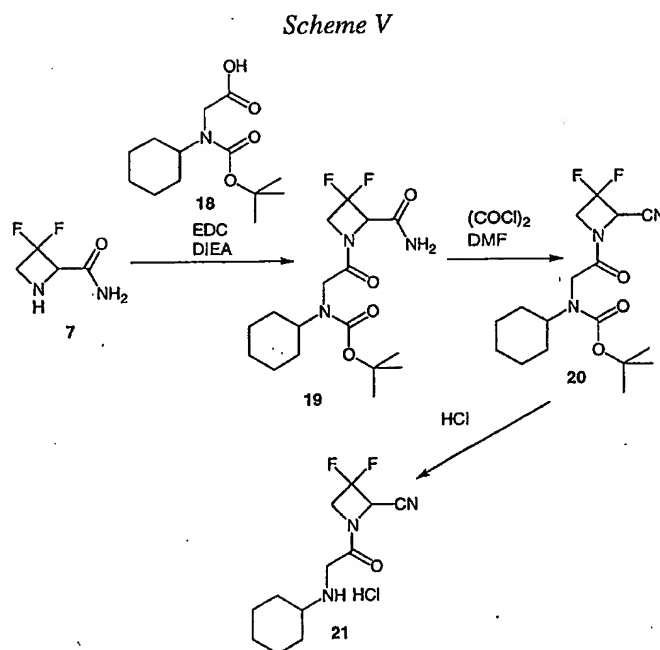
Synthesis of 1-(2-Cyclohexylaminoacetyl)-3,3-difluoroazetidine-2-carbonitrile

5 Hydrochloride (21, Scheme V):

The title compound is prepared according to the procedures of Scheme V, below.

- 10 1-[2-(N-(t-Butyloxycarbonylamino)-N-Cyclohexyl)aminoacetyl]-3,3-difluoroazetidine-2-carboxamide (19): This compound is prepared from the protected amino acid derivative 18 and amide 7 (Scheme III) according to the procedure given above for amide 8 (see Scheme III, above). White solid; expected yield 66%.

- 15 1-[2-(N-(t-Butyloxycarbonylamino)-N-Cyclohexyl)aminoacetyl]-3,3-difluoroazetidine-2-carbonitrile (20): The compound is prepared according to the procedure given above for the nitrile 9.(see Scheme III, above) Yellowish wax; expected yield 55%.

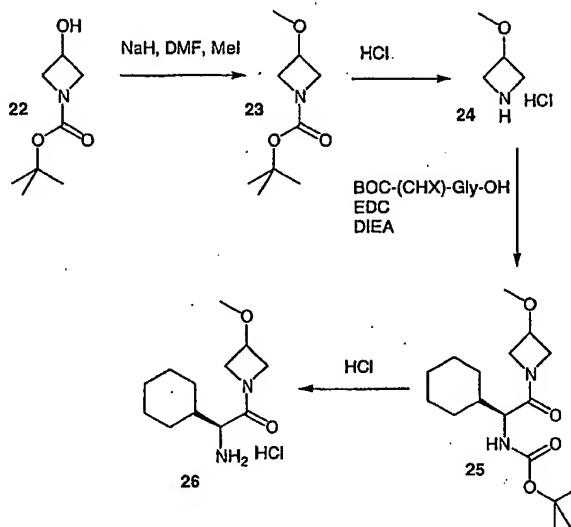


- 20 1-(2-Cyclohexylaminoacetyl)-3,3-difluoroazetidine-2-carbonitrile Hydrochloride (21): This compound is prepared according to the procedure given above for compound 10 (see Scheme III, above). White hygroscopic solid; expected yield 96%.

Synthesis of 2-Amino-2-cyclohexyl-1-(3-methoxyazetidin-1-yl)-ethanone hydrochloride (26, Scheme VI): The title compound is prepared according to the procedures of Scheme VI, below.

5

Scheme VI



The 3-Methoxy-substituted azetidine derivative **26** is prepared from the corresponding starting material **22** via alkylation in the presence of NaH to produce the intermediate **23** according to procedures which are themselves well-established in the art (see, e.g. Falguyret, J.-P., et al. *J. Med. Chem.*, 2001, Vol.44, pp 94-104). This intermediate is further deprotected by HCl solution in dioxane, as described above for the preparation of compounds **10** and **17** (see Schemes III, IV). The amine **24** thus obtained is coupled with L-N-BOC-(alfa-cyclohexyl)glycine in a manner analogous to the preparation of compound **8**, above (see Scheme III), using EDC as a coupling agent, and DIEA as a base. Finally, deprotection is done yet again similarly to the preparation of compounds **10** and **17** (see Schemes III, IV, above).

As will be appreciated by one skilled in the art, other 3-(alkoxy) substituted azetidines can be prepared in analogous ways, by varying the type of alkylating agent utilized in the first step (conversion of compound **22** into **23**).

20

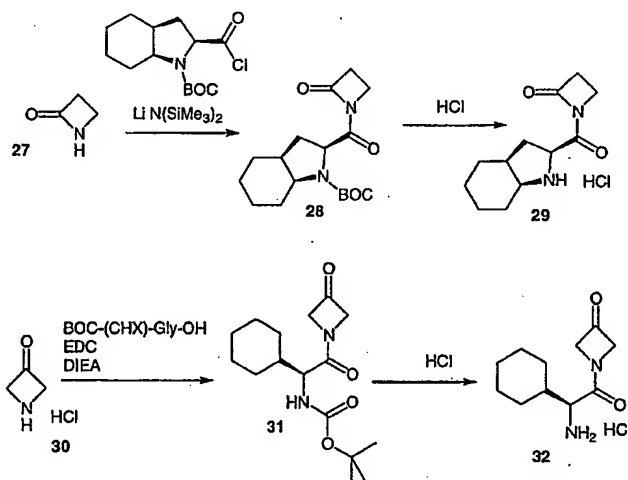
Synthesis of 1-(Octahydro-indole-2-carbonyl)-azetidin-2-one (29) and 1-(2-amino-2-cyclohexylacetyl)-azetidin-3-one (32, Scheme VII): The title compound is prepared according to the procedures of Scheme VII, below.

- 5 The azetidin-2-one derivative **29** is prepared by reacting azetidin-2-one **27** with lithium hexamethyldisilazane to form the corresponding anion, followed by acylation with N-BOC-OIC-Cl, in accordance with procedures which are themselves well-established in the art (*see, e.g.,* Gerard, S. et al., *Tetrahedron*, 2002, Vol.58, No.12, pp. 2423-2434). Deprotection is further conducted analogously to the procedures given above for
- 10 compounds **10** and **17** (*see* Schemes III, IV, above).

The azetidin-3-one derivative **32** is prepared by a standard coupling procedure from amine hydrochloride **30**, analogous to the above-described transformation of compound **24** into **25** and finally into **26** (*see* Scheme VI).

15

Scheme VII



- 20 Other amino acids may also be employed in the preparation of analogs of compounds **26**, **29**, and **32**. The preparation of such analogues, and that of other specific compounds across the full scope of Formula I, can be conducted by the ordinary artisan based on the guidance provided herein, the recited examples and procedures, and the cited references,

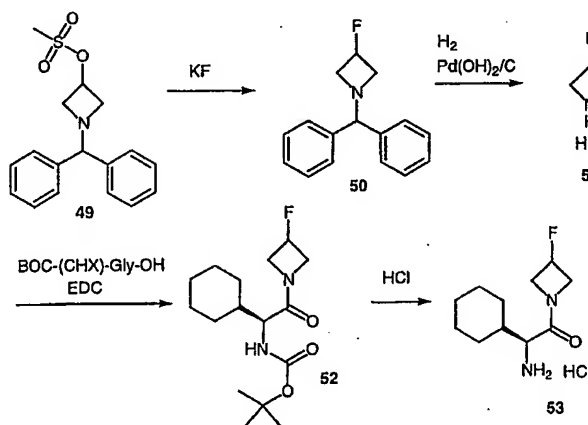
all viewed in light of the present state of the pharmaceutical and chemical arts, as will be appreciated by those of ordinary skill in these arts.

Preparation of 2-amino-2-cyclohexyl-1-(3-fluoroazetidin-1-yl)-ethanone hydrochloride (compound 53, Scheme VIII):

The title compound was prepared according to the procedures given in scheme VIII, below.

- 1-Benzhydryl-3-fluoroazetidine (50): Methanesulfonic acid 1-benzhydryl-azetidin-3-yl ester (49, 6.0 g, 0.019 mol), KF (7.5 g, 0.13 mol, and diethylene glycol (110 mL) were stirred and heated at 85 °C under argon overnight. The reaction mixture was poured into ice-water (100 g), stirred briefly, and partitioned between water (50 mL) and ethyl acetate (150 mL). It was then additionally extracted with ethyl acetate (2x150 mL). The combined organic layers were dried, solvents evaporated in vacuum, and the residue was purified by flash column chromatography (silica gel, eluent - 7:3 hexanes/ethyl acetate). Light oil; yield 1.8 g (39%).
- ¹H NMR (CDCl₃), δ: 7.41-7.17 (m, 10H), 5.26-5.22(m, 0.5H), 5.07-5.03(m, 0.5H), 4.38(s, 1H), 3.59-3.51(m, 2H), 3.20-3.10(m, 2H).

Scheme VIII



- 3-Fluoroazetidine hydrochloride (51): 1-Benzhydryl-3-fluoro-azetidine (50, 1.8 g, 0.0075 mol), Pd(OH)₂ on carbon (0.5 g) and HCl in dioxane (4M solution, 3.0 mL) were placed

in a Parr hydrogenation flask. Methanol (100 mL) was added, and the whole was hydrogenated at 50 psi and room temperature overnight. The mixture was filtered through a Celite plug, the solvent was evaporated from the filtrate, and the solid residue was washed with ether (30 mL), benzene (30 mL), and dichloromethane (30 mL) to afford a white hygroscopic solid; yield 0.65g (78%).

¹H NMR (D₂O), δ: 5.48-5.42(m, 0.5H), 5.32-5.23(m, 0.5H), 4.47-4.34(m, 2H), 4.27-4.15(m, 2H).

[1-Cyclohexyl-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]carbamic acid t-butyl ester (52): To a stirred suspension of 3-fluoroazetidine hydrogen chloride (51, 0.10 g, 0.0009 mol), diisopropylethylamine (0.25g, 0.0020 mol), N,N-dimethylaminopyridine (10 mol.%), and L-N-BOC-(cyclohexyl)glycine (0.28g, 0.0011 mol) in dichloromethane (3 mL) was added EDC (0.21g, 0.0011 mol) at room temperature. After stirring at room temperature overnight, dichloromethane (10 mL) and NaHCO₃ (sat., 5 mL) were added. Upon extraction, the organic layer was subsequently washed with NaHCO₃ (2x3 mL), KHSO₄ (5 % 2x3 mL) and saline (3 mL). The organic layer was separated, dried, solvents were evaporated, and the residue was purified by flash column chromatography (silica, eluent: 1:1 hexanes/ethyl acetate). Yellowish oil; yield 0.25g (89%). MS (+): 315.

2-Amino-2-cyclohexyl-1-(3-fluoroazetidin-1-yl)ethanone hydrochloride (53): [1-Cyclohexyl-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]-carbamic acid *tert*-butyl ester (52, 0.10 g, 0.00032 mol) was dissolved in HCl/dioxane (1.5 mL, 4M solution). The reaction mixture was stirred under argon at room temperature for 1.5 h (TLC indicated the absence of the starting material). Solvent was removed in vacuum to afford a white solid, which was quickly washed by ether (3x3 mL). The title compound was obtained as a white hygroscopic solid; yield 0.064g (80%). ¹H NMR (D₂O), δ: 5.50-5.40 and 5.29-5.20 (m, 1H), 4.64-4.01(m, 4H), 3.80-3.78(d, J=6.0 Hz, 1H), 1.72-1.57(m, 6H), 1.20-1.00(m, 5H). MS+:215.

As those of ordinary skill in the chemical and pharmaceutical arts will appreciate, the procedures of Schemes I – VIII, above, and the guidance provided herein, singly or together with the recited references, when viewed in the context of the present state of the art, allow one to create many modifications of the compounds of the present invention

across the full scope of formula I. Thus, the specific compounds described in schemes I – VIII above, in table I below, and throughout this specification, while being in themselves useful in the methods and compositions of the invention, provide specific examples of compounds of formula I which are intended to illustrate the instant invention and to

5 provide those of ordinary skill with guidance for the design and synthesis of yet other useful compounds of formula I. It will therefore be understood that the present invention is not limited to the specific illustrative compounds of formula I recited herein. Specific examples of such illustrative compounds, which can be prepared in accordance with the above procedures, and which are in themselves useful in the methods and compositions

10 of the instant invention, include the following:

Table Ia

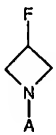
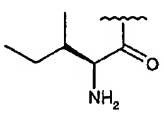
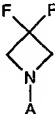
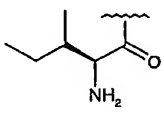
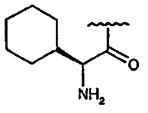
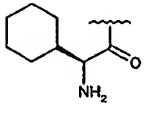
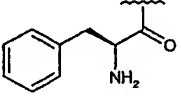
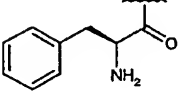
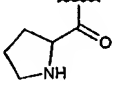
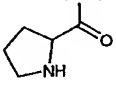
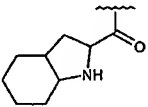
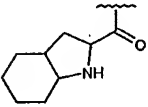
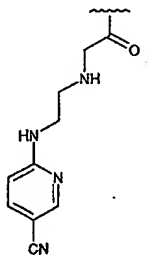
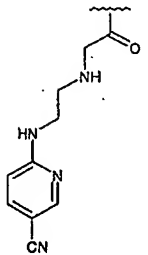
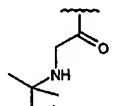
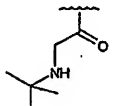
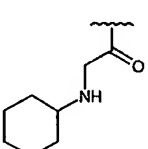
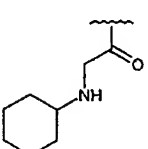
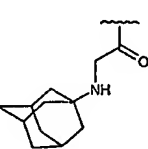
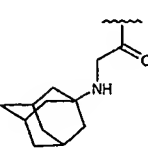
Compound no.		A:	Compound no.		A:
54			63		
53			64		
56			65		
57			66		
58			67		
59			68		
60			69		
61			70		
62			71		

Table Ib

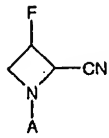
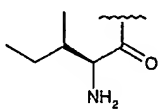
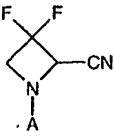
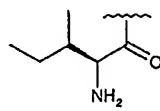
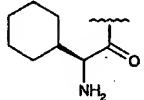
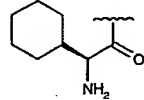
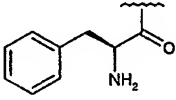
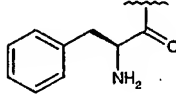
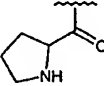
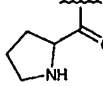
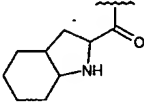
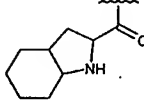
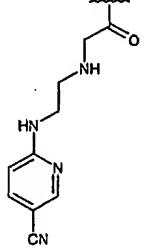
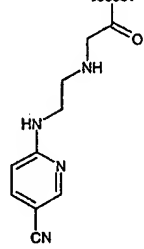
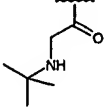
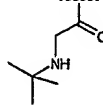
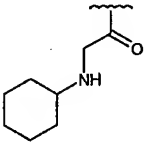
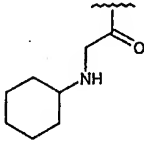
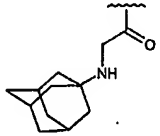
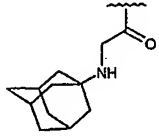
Compound no.		A:	Compound no.		A:
72			81		
73			82		
74			83		
75			84		
76			85		
77			86		
78			87		
79			21		
80			89		

Table Ic

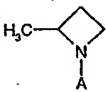
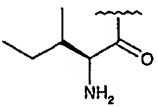
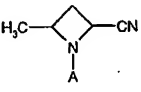
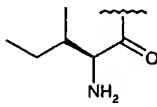
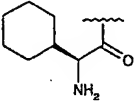
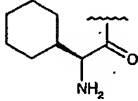
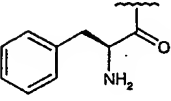
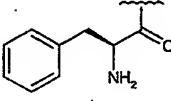
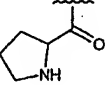
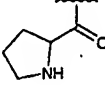
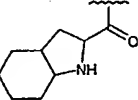
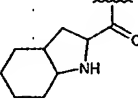
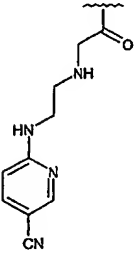
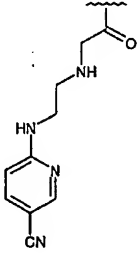
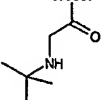
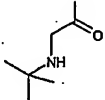
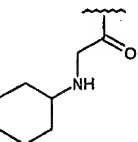
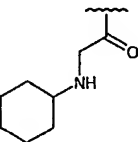
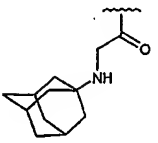
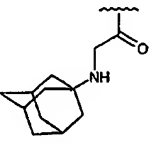
Compound no.		A:	Compound no.		A:
90			99		
91			48		
92			101		
93			102		
94			42		
95			104		
96			47		
97			106		
98			107		

Table Id

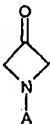
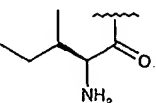

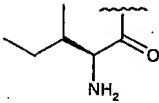
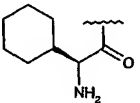
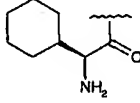
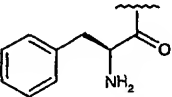
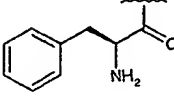
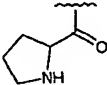
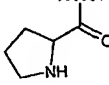
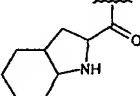
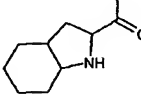
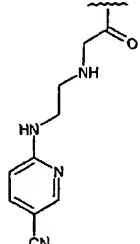
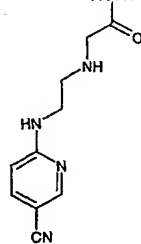
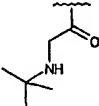
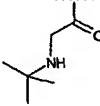
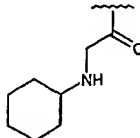
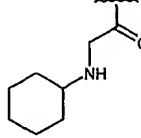
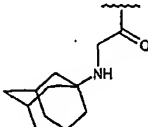
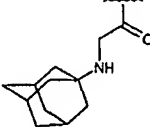
Compound no.		A:	Compound no.		A:
108			117		
32			118		
110			119		
111			120		
112			121		
113			122		
114			123		
115			124		
116			125		

Table Ia

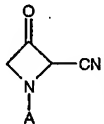
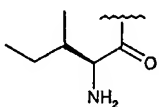
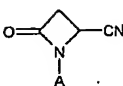
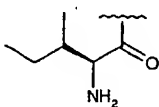
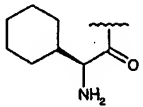
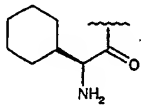
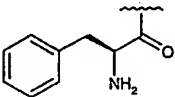
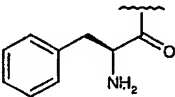
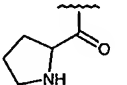
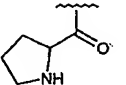
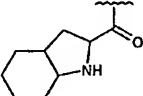
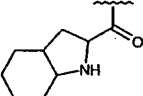
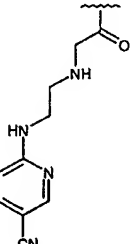
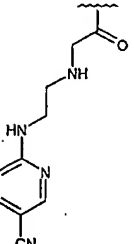
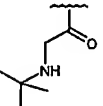
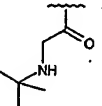
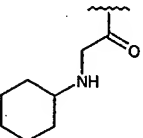
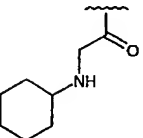
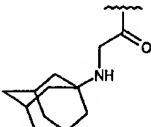
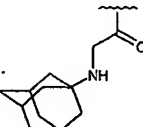

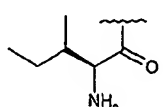
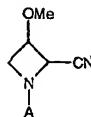
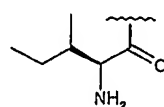
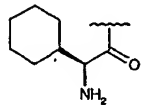
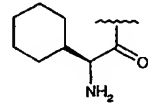
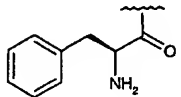
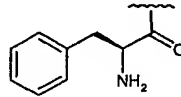
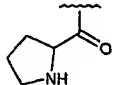
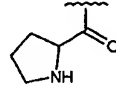
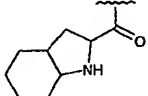
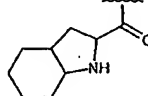
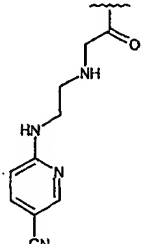
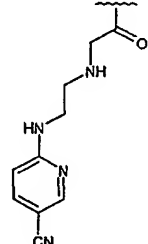
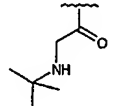
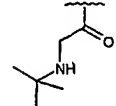
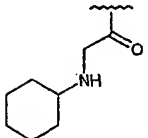
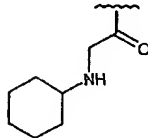
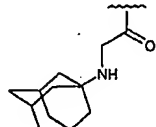
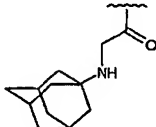
Compound no.		A:	Compound no.		A:
126			135		
127			136		
128			137		
129			138		
130			139		
131			140		
132			141		
133			142		
134			143		

Table If

Compound no.		A:	Compound no.		A:
144			153		
26			154		
146			155		
147			156		
148			157		
149			158		
150			159		
151			160		
152			161		

Measuring the Bioactivity of the Compounds of the Invention:

As noted above, a number of methods can be used to assay for the bioactivity of the compounds of the invention. Appropriate assays can be *in vivo* or *in vitro* methods, which are themselves well-established in the art. For example, to determine the efficacy of the compounds of Formula I in the treatment or prevention of diabetes, the Zucker Diabetic rat model can be utilized, as will be appreciated by one skilled in the art. Rats of the Zucker strain are initially pre-diabetic, but develop a type II diabetes of varying severity as they mature. The literature cited herein discloses many such assays, and can be relied upon to make and practice aspects of the instant invention. The examples below illustrate assays that allow one to determine the ability of the compounds to produce an anti-inflammatory effect, an analgesic effect, or to protect neuronal cells from toxic treatments and the ability of the compounds to elicit neuronal cell growth, regeneration, or neurite extension.

Measuring DPP IV inhibition:

The inhibitory activity of the compounds of Formula I against DPP IV can be determined by *in vitro* assay systems which are themselves well-established in the art. For example, inhibitory constants of the compounds of this invention can be determined by testing the compounds on purified porcine DPP IV according to the method taught at columns 23 – 24 of U.S. patent 6,395,762 to Robl *et al.*, which method is hereby incorporated by reference.

The inhibitory potency of the compounds of this invention can also be evaluated by determining the concentration of test compound, which causes a 50% reduction in DPP IV activity *in vitro* (IC₅₀). A simple assay method for the determination of such IC₅₀ values is as follows:

One volume of rat plasma (coagulated with sodium citrate) is diluted 15x with assay buffer (25 mM HEPES, 20 mM MgCl₂, 140 mM NaCl, 1% BSA [added on the day of the assay]; pH 7.8) to yield approximately 350 micrograms total protein/well in a 96-well plate. Dilute the peptide substrate (H-Gly-Pro- α methyl coumarin, 10 mM stock in 100% dimethyl sulphoxide (DMSO) 1:50 in assay buffer. Compounds of this invention are diluted in 100% DMSO. Add 50 μ L of peptide substrate to wells (no vortexing); then add 10 μ L of diluted compounds or DMSO vehicle to wells. Start the reaction by adding 40 μ L of rat plasma or buffer to wells, and incubate the plate at room temp in the dark for 30 minutes. Stop the reaction by adding 25 μ L of 25% glacial acetic

acid. Read the plate at 380 nm (excitation) and 460 nm (emission). Plot fluorescence vs. concentration of test compound to determine the concentration of test compound which yields a 50% inhibition of DPP IV enzymatic activity (IC_{50}). Exemplary IC_{50} values for above-described specific compounds of this invention were determined to be: 200 nM for compound 48; 200 nM for compound 46; 600 nM for compound 47; and 500 nM for compound 42.

Neuroprotection Assay in Spinal Cord Slice Preparations:

All cultures are derived from postnatal day 8 (P8) Sprague-Dawley rat lumbar spinal cord slices of 325 micron thickness, prepared using a commercially available McIlwain tissue chopper. Experiments consist of two 6-well plates with 5 slices from 4 different animals per well; slices are cultured at the media/atmosphere interface on a commercially available permeable membrane culture well insert. Media changes are performed every 3 to 4 days. Cultures are treated with the neurotoxin THA [L(-)-threo-3-hydroxyaspartic acid; Tocris Cookson Inc., Ballwin, Missouri] at 200 μ M + compound (10 μ M) after one week in culture. The control is an untreated sample with 0.1% DMSO as vehicle. The THA control is a THA treated sample with 0.1% DMSO as vehicle. Two wells are used per condition. One media change with new THA and compounds is performed. The experiment is stopped 6 to 8 days following drug treatment (13-15 total days in vitro, DIV) as dictated by visual assessment of lesion, by fixation with 4% paraformaldehyde/0.1 M phosphate buffer for 30 minutes. Slices are permeabilized with 100% cold methanol for 10 minutes and transferred to staining wells. The slices are blocked with 10% HS/TBS (horse serum/tris-buffered saline). Primary antibody incubation is overnight at 4°C with SMI-32 antibody 1:5000 in 2% HS/TBS. SMI-32 is specific towards the unphosphorylated H neurofilament subunit. Vectastain ABC Elite Kit with rat absorbed anti-mouse secondary antibody is used with 3,3-diaminobenzidine as a chromogen to stain the slices. The slices are mounted onto a slide and a coverslip is sealed with DPX mounting solution.

Quantification of surviving neurons is performed on a Zeiss Axiovert microscope. Neuronal survival is determined by observing an intact neuronal cell body with processes located ventrally of the central canal in each hemisphere. This correlates to laminae VII, VIII and IX. Each hemisphere is counted individually. Statistical analysis is performed with StatView™ software on a minimum of three different experiments per condition and

significance is determined as compared to THA control. The percent of protection is determined from the average number of living neurons by the following equation: (drug treatment condition – THA control)/(Untreated control-THA control).

THA-treated control cultures display a significantly reduced average number of
5 SMI-32 immunoreactive neurons per ventral hemisphere of the spinal cord slices at the end of the culturing interval, as compared to untreated control cultures. Addition of the compounds of this invention to THA-treated cultures causes a significant protection from THA-induced cell death.

10 Antiinflammatory effects

The anti-inflammatory activity of the compounds of formula I can be assessed in the carrageenan-induced hindpaw inflammation model in the rat, which has long been established in the art [see, e.g., Winter, et al., Proc. Soc. Exp. Biol. Med. 111 (1962) 544-547]. Carrageenan is a naturally-occurring family of carbohydrates extracted from red
15 seaweed, which is commercially available for experimental purposes and is known to trigger a strong inflammatory and edema response following injection. Briefly, male albino rats of the Wistar or Sprague-Dawley strains are housed under a 12 h light/dark cycle with free access to food and water. For testing anti-inflammatory activity, the compound of formula I is dissolved in physiological saline or another pharmaceutically
20 acceptable vehicle and dosed i.p. one hour before, and two hours following carrageenan injection. Control animals receive i.p. injections of vehicle only. Carrageenan is injected into the intraplantar region of the right hindpaw (0.75 mg per paw in 0.05 ml physiological saline). For intra-animal control, the contralateral hindpaw receives a similar injection of vehicle alone. At four hours following carrageenan injection, animals
25 are euthanized and the inflammatory response to carrageenan injection is assessed by volumetric measurement of hindpaw edema. Relative to control animals, animals treated with compounds of formula I display a dose-dependent attenuation of carrageenan-induced hindpaw swelling.

30 Analgesic effects

The analgesic effects of the compounds of this invention can be established by methods which are themselves well-established in the art [see, e.g., Hunskaar et al., J. Neurosci. Methods 14 (1985) 69-76]. A simple analgesia assay useful in assessing efficacy of the compounds of formula I employs subcutaneous formalin injections in

mice dosed with the compounds of this invention. Briefly, male albino NMRI mice (30-45 g) are housed under a 12h light/dark cycle with access to food and water *ad libitum*. The test compound of formula I is dissolved in sterile saline or other pharmaceutically suitable vehicles and dosed i.p. 30 min. prior to subcutaneous injection of a formalin solution under the dorsal surface of the right hindpaw (20 microliters of a 1 or 5% w/v solution in saline or another pharmaceutically suitable vehicle). The animal is then observed and the time spent licking the injected hindpaw is recorded. Control animals receive only vehicle injections. Pain intensity is rated using one single objective response: licking the injected paw, either the dorsal surface of the paw, the toes, or the leg.

Subcutaneous formalin injection results in a biphasic behavioral response, where the experimental animal spends time licking the injected hindpaw during the first 5-10 minutes following formalin injection, then displays diminished licking activity for the following 5 – 10 minutes, followed by a second, late pain response during the following 20 – 30 minutes.

Compared to animals dosed intraperitoneally with vehicle only, mice dosed with compounds of formula I display a dose-dependent reduction in either the early or late-phase licking response, or both the early- and late-phase licking response, to subcutaneous formalin injection.

Antipsychotic effects

The antipsychotic effects of the compounds of the invention can be determined by established methods, such as, for example the mescaline-induced "scratching" model [see, e.g., Cook *et al.*, J. Pharmacol. Exp. Ther. 263 (1992) 1159-66]: Young adult Swiss-Webster albino male mice receive parenteral injections of a compound of Formula I (1 – 100 mg/kg) or vehicle, followed 30 minutes later by i.p. injection of mescaline (50 mg/kg). Mice (n = 10 – 15/group) are then placed in individual cages and monitored for onset of scratching behavior. Beginning 20 minutes after the injection of mescaline, the numbers of back and neck scratching episodes are counted by a naïve observer over a 5 minute period. Compared to control animals, pretreatment with the compounds of the invention significantly reduces the number of compulsive scratching episodes induced by mescaline in mice.

Yet another model known in the art to be useful for assessing antipsychotic activity of experimental compounds is the amphetamine-induced locomotor hyperactivity model in mice: Young adult male albino mice receive parenteral injections of a compound of Formula I (1 – 100 mg/kg) or vehicle, followed 30 min. later by i.p.

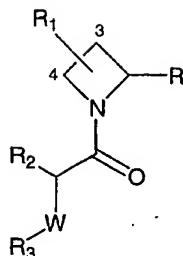
- 5 injections of a locomotor stimulatory dose of dexamphetamine sulphate (3 mg/kg i.p.). Immediately following amphetamine injection, mice are individually placed in automated behavioral activity chambers, and open-field locomotor activity is measured over a 30 min. period. Compared to amphetamine-treated animals that are pretreated with vehicle alone, amphetamine-treated mice that are pretreated with the compound of Formula I
- 10 display a significant reduction in open-field activity, indicating that the compound of Formula I is capable of antagonizing the locomotor stimulatory effects of amphetamine *in vivo*.

15

- The invention being thus described, it will be obvious that the same may be varied in many ways. The specific examples disclosed herein should not be interpreted as a limitation on the scope of the invention. Instead, they are merely exemplary embodiments
- 20 one skilled in the art would understand from the entire disclosure of this invention. The many variations of this invention, which one of skill in the art can create based on the examples and guidance provided herein, are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be within the scope of the following claims.

We claim:

1. A compound of Formula I:



Formula I

or pharmaceutically acceptable derivatives thereof; wherein

R is H or CN;

R1 is F, di-F, (=O), CN, alkoxy, or alkyl, and is attached at position 3 or 4;

W is NH, or CH₂;

wherein, when W is NH:

- (i.) one of R2 and R3 is hydrogen, and the other of R2 and R3 is
 - a C₁-C₁₂ straight or branched chain alkyl; or
 - a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or
 - a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms; or
- (ii.) R2 and R3, together with W and the carbon atom to which they are attached, form a four- to twelve-membered saturated ring, said ring optionally having fused thereto one or two additional rings independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂ cycloalkenyl, aryl, and heteroaryl; and

wherein, when W is CH₂:

R2 and R3, together with W and the carbon atom to which they are attached, form a four- to twelve-membered heterocyclic ring, said ring containing at least one nitrogen immediately adjacent to W, said ring optionally having fused thereto one or two additional

rings independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂ cycloalkenyl, aryl, and heteroaryl;

provided that: when R is H, R1 is not CN attached at position 4;

and further provided that: when R is CN; and R1 is F or CN attached at position 3; and W is NH; then R3 is not adamantyl, bicyclooctyl, or 2-[(5-cyano-2-pyridyl)amino]ethyl.

2. The compound of **claim 1**, wherein R is CN, and R1 is F or di-F
3. The compound of **claim 2**, wherein said F or di-F is attached at position 3.
4. The compound of **claim 2**, wherein W is NH.
5. The compound of **claim 4**, wherein R3 is H, and R2 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.
6. The compound of **claim 4**, wherein R2 is H and R3 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.
7. The compound of **claim 4**, wherein R2 and R3, together with W and the carbon atom to which they are attached, form a four- to twelve-membered saturated ring, said ring optionally having fused thereto one or two additional rings independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂ cycloalkenyl, aryl, and heteroaryl.
8. The compound of **claim 2**, wherein W is CH₂.
9. The compound of **claim 8**, wherein R1 is attached at position 3.
10. The compound of **claim 1**, wherein R is CN and R1 is (=O).
11. The compound of **claim 10**, wherein W is NH.
12. The compound of **claim 11**, wherein R3 is H, and R2 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.
13. The compound of **claim 11**, wherein R2 is H and R3 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.

14. The compound of **claim 11**, wherein R2 and R3, together with W and the carbon atom to which they are attached, form a four- to twelve-membered saturated ring, said ring optionally having fused thereto one or two additional rings independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂ cycloalkenyl, aryl, and heteroaryl.
15. The compound of **claim 10**, wherein W is CH₂.
16. The compound of **claim 1**, wherein R is CN and R1 is CN.
17. The compound of **claim 16**, wherein W is NH.
18. The compound of **claim 17**, wherein R3 is H, and R2 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.
19. The compound of **claim 17**, wherein R2 is H and R3 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.
20. The compound of **claim 17**, wherein R2 and R3, together with W and the carbon atom to which they are attached, form a four- to twelve-membered saturated ring, said ring optionally having fused thereto one or two additional rings independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂ cycloalkenyl, aryl, and heteroaryl.
21. The compound of **claim 16**, wherein W is CH₂.
22. The compound of **claim 1**, wherein R is CN and R1 is alkoxy or alkyl.
23. The compound of **claim 22**, wherein said alkoxy or alkyl is methoxy or methyl.
24. The compound of **claim 23**, wherein W is NH.
25. The compound of **claim 24**, wherein R3 is H, and R2 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.
26. The compound of **claim 24**, wherein R2 is H and R3 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.

27. The compound of **claim 24**, wherein R2 and R3, together with W and the carbon atom to which they are attached, form a four- to twelve-membered saturated ring, said ring optionally having fused thereto one or two additional rings independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂ cycloalkenyl, aryl, and heteroaryl.
28. The compound of **claim 23**, wherein W is CH₂.
29. The compound of **claim 1**, wherein R is H and R1 is F or di-F.
30. The compound of **claim 29**, wherein said F or di-F is attached at position 3.
31. The compound of **claim 29**, wherein W is NH.
32. The compound of **claim 31**, wherein R3 is H, and R2 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.
33. The compound of **claim 31**, wherein R2 is H and R3 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.
34. The compound of **claim 31**, wherein R2 and R3, together with W and the carbon atom to which they are attached, form a four- to twelve-membered saturated ring, said ring optionally having fused thereto one or two additional rings independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂ cycloalkenyl, aryl, and heteroaryl.
35. The compound of **claim 29**, wherein W is CH₂.
36. The compound of **claim 35**, wherein R1 is attached at position 3.
37. The compound of **claim 1**, wherein R is H and R1 is (=O).
38. The compound of **claim 37**, wherein W is NH.
39. The compound of **claim 38**, wherein R3 is H, and R2 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.
40. The compound of **claim 38**, wherein R2 is H and R3 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.

41. The compound of **claim 38**, wherein R2 and R3, together with W and the carbon atom to which they are attached, form a four- to twelve-membered saturated ring, said ring optionally having fused thereto one or two additional rings independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂ cycloalkenyl, aryl, and heteroaryl.
42. The compound of **claim 37**, wherein W is CH₂.
43. The compound of **claim 1**, wherein R is H and R1 is CN attached at position 3.
44. The compound of **claim 43**, wherein W is NH.
45. The compound of **claim 44**, wherein R3 is H, and R2 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.
46. The compound of **claim 44**, wherein R2 is H and R3 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.
47. The compound of **claim 44**, wherein R2 and R3, together with W and the carbon atom to which they are attached, form a four- to twelve-membered saturated ring, said ring optionally having fused thereto one or two additional rings independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂ cycloalkenyl, aryl, and heteroaryl.
48. The compound of **claim 43**, wherein W is CH₂.
49. The compound of **claim 1**, wherein R is H and R1 is alkoxy or alkyl.
50. The compound of **claim 49**, wherein said alkoxy or alkyl is methoxy or methyl.
51. The compound of **claim 50**, wherein W is NH.
52. The compound of **claim 51**, wherein R3 is H, and R2 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.
53. The compound of **claim 51**, wherein R2 is H and R3 is a C₁-C₁₂ straight or branched chain alkyl; or a C₁-C₆ straight or branched chain alkyl substituted with aryl, arylamino, heteroaryl, or heteroarylamino; or a saturated mono- bi- or tricyclic hydrocarbon wherein the individual rings comprise 3 – 12 carbon atoms.

54. The compound of **claim 51**, wherein R2 and R3, together with W and the carbon atom to which they are attached, form a four- to twelve-membered saturated ring, said ring optionally having fused thereto one or two additional rings independently selected from C₄-C₁₂ cycloalkyl, C₄-C₁₂ cycloalkenyl, aryl, and heteroaryl.
55. The compound of **claim 50**, wherein W is CH₂.
56. A pharmaceutical composition, comprising a compound of Formula I as defined in claim 1, and a pharmaceutically acceptable carrier, diluent, or excipient.
57. A method of treatment, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I as defined in claim 1, wherein said patient suffers from, or is at risk for, a medical condition which can be alleviated by inhibition of DPP IV.
58. A method of treatment, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I as defined in claim 1, wherein said patient suffers from, or is at risk for, a medical condition selected from the group consisting of neurological disorder, mental illness, inflammatory disorder, pain disorder, diabetes, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of free fatty acids or glycerol, obesity, hypertriglyceridemia, atherosclerosis, impaired glucose tolerance, impaired glucose homeostasis, polycystic ovary syndrome, arthritis, allograft rejection in organ or tissue transplantation, autoimmune disorder, AIDS, inflammatory bowel disease, osteoporosis, psoriasis, metastatic cancer, and rheumatoid arthritis.